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<p>(21) International Application Number: PCT/US00/09753</p> <p>(22) International Filing Date: 12 April 2000 (12.04.00)</p> <p>(30) Priority Data: 60/129,510 15 April 1999 (15.04.99) US</p> <p>(71) Applicant: BRISTOL-MYERS SQUIBB CO. [US/US]; P.O. Box 4000, Princeton, NJ 08543-4000 (US).</p> <p>(72) Inventors: DAS, Jagabandhu; 38 Martin Lane, Mercerville, NJ 08619 (US). PADMANABHA, Ramesh; 80 Carmel Street, Hamden, CT 06518 (US). CHEN, Ping; 21 Derby Chase Court, Belle Mead, NJ 08502 (US). NORRIS, Derek, J.; 52 Manley Road, Trenton, NJ 08638 (US). DOWEYKO, Arthur, M., P.; 9 Highland Avenue, Long Valley, NJ 07853 (US). BARRISH, Joel, C.; 46 Heather Valley Road, Holland, PA 18966 (US). WITYAK, John; 25 Jared Drive, Robbinsville, NJ 08691 (US).</p> <p>(74) Agents: HERMENAUI, Ronald, S. et al.; Bristol-Myers Squibb Co., P.O. Box 4000, Princeton, NJ 08543-4000 (US).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: CYCLIC PROTEIN TYROSINE KINASE INHIBITORS</p> <p>(57) Abstract</p> <p>Novel cyclic compounds and salts thereof, pharmaceutical compositions containing such compounds, and methods of using such compounds in the treatment of protein tyrosine kinase-associated disorders such as immunologic and oncologic disorders.</p>		

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CYCLIC PROTEIN TYROSINE KINASE INHIBITORS

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Field of the Invention

The present invention relates to cyclic compounds and salts thereof,
10 to methods of using such compounds in treating protein tyrosine kinase-associated disorders such as immunologic and oncologic disorders, and to pharmaceutical compositions containing such compounds.

Background of the Invention

15 Protein tyrosine kinases (PTKs) are enzymes which, in conjunction with ATP as a substrate, phosphorylate tyrosine residues in peptides and proteins. These enzymes are key elements in the regulation of cell signaling including cell proliferation and cell differentiation. PTKs comprise, *inter alia*, receptor tyrosine kinases (RPTKs), including
20 members of the epidermal growth factor kinase family (e.g., HER1 and HER2), platelet derived growth factor (PDGF), and kinases that play a role in angiogenesis (Tie-2 and KDR); and, in addition, non-receptor tyrosine kinases, including members of the Syk, JAK and Src (e.g. Src, Fyn, Lyn, Lck and Blk) families (see Bolen, J.B., Rowley, R.B., Spana, C.,
25 and Tsygankov, A.Y., "The src family of tyrosine protein kinases in hemopoietic signal transduction", *FASEB J.*, 6, 3403-3409 (1992); Ullrich, A. and Schlessinger, J., "Signal transduction by receptors with tyrosine kinase activity", *Cell*, 61, 203-212 (1990); and Ihle, J.N., "The Janus protein tyrosine kinases in hematopoietic cytokine signaling", *Sem.*
30 *Immunol.*, 7, 247-254 (1995)).

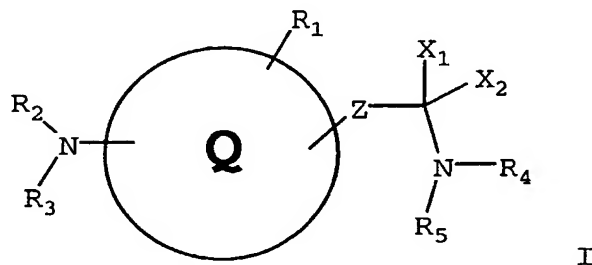
Enhanced activity of PTKs has been implicated in a variety of malignant and nonmalignant proliferative diseases. In addition, PTKs play a central role in the regulation of cells of the immune system. PTK inhibitors can thus impact a wide variety of oncologic and immunologic disorders. Such disorders may be ameliorated by selective inhibition of a certain receptor or non-receptor PTK, such as Lck, or due to the homology among PTK classes, by inhibition of more than one PTK by an inhibitor.

A PTK of particular interest is Lck which is found in T cells where it is involved in phosphorylating key protein substrates. It is required for productive antigen receptor signaling and cell activation. In the absence of Lck activity, the T cell receptor (TCR) zeta chain is not phosphorylated, the kinase ZAP-70 is not activated, and Ca^{2+} mobilization essential for T cell activation does not occur (see Weiss, A. and Littman, D.R., "Signal transduction by lymphocyte antigen receptors", *Cell*, 76, 263-274 (1994); Iwashima, M., Irving, B.A., van Oers, N.S.C., Chan, A.C., and Weiss, A., "Sequential interactions of the TCR with two distinct cytoplasmic tyrosine kinases", *Science*, 263, 1136-1139 (1994); and Chan, A.C., Dalton, M., Johnson, R., Kong, G., Wang, T., Thoma, R., and Kurosaki, T., "Activation of ZAP-70 kinase activity by phosphorylation of tyrosine 493 is required for lymphocyte antigen receptor function", *EMBO J.*, 14, 2499-2508 (1995)). Inhibitors of Lck are thus useful in the treatment of T-cell mediated disorders such as chronic diseases with an important T cell component, for example rheumatoid arthritis, multiple sclerosis and lupus, as well as acute diseases where T cells are known to play an essential role, for example acute transplant rejection and delayed-type hypersensitivity (DTH) reactions.

Summary of the Invention

The present invention provides cyclic compounds of the following formula I and salts thereof, for use as protein tyrosine kinase inhibitors:

5



where

10 Q is:

- (1) a 5-membered heteroaryl ring;
 - (2) a 6-membered heteroaryl ring; or
 - (3) an aryl ring;
- optionally substituted with one or more groups R_1 ;

15 Z is:

- (1) a single bond;
- (2) $-R_{15}C=CH-$; or
- (3) $-(CH_2)_m-$, where m is 1 to 2;

20 X_1 and X_2 are each hydrogen, or together form $=O$ or $=S$;

R_1 is:

- (1) hydrogen or R_6 ,

where R_6 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aralkyl, heterocyclo, or heterocycloalkyl, each of which is unsubstituted or substituted with Z_1 , Z_2 and one or more (preferably, one or two) groups Z_3 ;

25

- (2) -OH or -OR₆;
- (3) -SH or -SR₆;
- (4) -C(O)₂H, -C(O)_qR₆, or -O-C(O)_qR₆, where q is 1 or 2;
- (5) -SO₃H or -S(O)_qR₆;
- 5 (6) halo;
- (7) cyano;
- (8) nitro;
- (9) -Z₄-NR₇R₈;
- (10) -Z₄-N(R₉)-Z₅-NR₁₀R₁₁;
- 10 (11) -Z₄-N(R₁₂)-Z₅-R₆;
- (12) -P(O)(OR₆)₂;

R₂ and R₃ are each independently:

- (1) hydrogen or R₆;
- (2) -Z₄-R₆; or
- 15 (3) -Z₁₃-NR₇R₈;

R₄ and R₅:

- (1) are each independently hydrogen or R₆;
- (2) -Z₄-N(R₉)-Z₅-NR₁₀R₁₁;
- (3) -N(R₉)Z₄R₆; or
- 20 (4) together with the nitrogen atom to which they are attached
complete a 3- to 8-membered saturated or unsaturated
heterocyclic ring which is unsubstituted or substituted
with Z₁, Z₂ and Z₃, which heterocyclic ring may
optionally have fused to it a benzene ring itself
- 25 unsubstituted or substituted with Z₁, Z₂ and Z₃;

R₇, R₈, R₉, R₁₀, R₁₁ and R₁₂:

- (1) are each independently hydrogen or R₆;
- (2) R₇ and R₈ may together be alkylene, alkenylene or
heteroalkyl, completing a 3- to 8-membered saturated
30 or unsaturated ring with the nitrogen atom to which

they are attached, which ring is unsubstituted or substituted with Z_1 , Z_2 and Z_3 ; or

- (3) any two of R_9 , R_{10} and R_{11} may together be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with Z_1 , Z_2 and Z_3 ;

R_{13} is:

- (1) cyano;
- (2) nitro;
- (3) $-NH_2$;
- (4) $-NHOalkyl$;
- (5) $-OH$;
- (6) $-NHOaryl$;
- (7) $-NHCOOalkyl$;
- (8) $-NHCOOaryl$;
- (9) $-NHSO_2alkyl$;
- (10) $-NHSO_2aryl$;
- (11) aryl;
- (12) heteroaryl;
- (13) $-Oalkyl$; or
- (14) $-Oaryl$;

R_{14} is:

- (1) $-NO_2$;
- (2) $-COOalkyl$; or
- (3) $-COOaryl$;

R_{15} is:

- (1) hydrogen;
- (2) alkyl;
- (3) aryl;
- (4) arylalkyl; or

(5) cycloalkyl;

Z_1 , Z_2 and Z_3 are each independently:

- (1) hydrogen or Z_6 , where Z_6 is (i) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aralkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl; (ii) a group (i) which is itself substituted by one or more of the same or different groups (i); or (iii) a group (i) or (ii) which is substituted by one or more of the following groups (2) to (16) of the definition of Z_1 , Z_2 and Z_3 ;
- (2) -OH or -O Z_6 ;
- (3) -SH or -S Z_6 ;
- (4) -C(O)_qH, -C(O)_q Z_6 , or -O-C(O)_q Z_6 ;
- (5) -SO₃H, -S(O)_q Z_6 ; or S(O)_qN(Z_9) Z_6 ;
- (6) halo;
- (7) cyano;
- (8) nitro;
- (9) - Z_4 -N Z_7 Z_8 ;
- (10) - Z_4 -N(Z_9)- Z_5 -N Z_7 Z_8 ;
- (11) - Z_4 -N(Z_{10})- Z_5 - Z_6 ;
- (12) - Z_4 -N(Z_{10})- Z_5 -H;
- (13) oxo;
- (14) -O-C(O)- Z_6 ;
- (15) any two of Z_1 , Z_2 , and Z_3 may together be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached; or
- (16) any two of Z_1 , Z_2 , and Z_3 may together be -O-(CH₂)_r-O-, where r is 1 to 5, completing a 4- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached;

Z_4 and Z_5 are each independently:

- (1) a single bond;
- (2) $-Z_{11}-S(O)_q-Z_{12}-$;
- (3) $-Z_{11}-C(O)-Z_{12}-$;
- 5 (4) $-Z_{11}-C(S)-Z_{12}-$;
- (5) $-Z_{11}-O-Z_{12}-$;
- (6) $-Z_{11}-S-Z_{12}-$;
- (7) $-Z_{11}-O-C(O)-Z_{12}-$; or
- (8) $-Z_{11}-C(O)-O-Z_{12}-$;

10 Z_7 , Z_8 , Z_9 and Z_{10} :

- (1) are each independently hydrogen or Z_6 ;
- (2) Z_7 and Z_8 , or Z_6 and Z_{10} , may together be alkylene or
 alkenylene, completing a 3- to 8-membered saturated
 or unsaturated ring together with the atoms to which
 15 they are attached, which ring is unsubstituted or
 substituted with Z_1 , Z_2 and Z_3 ; or
- (3) Z_7 or Z_8 , together with Z_9 , may be alkylene or alkenylene
 completing a 3- to 8-membered saturated or
 unsaturated ring together with the nitrogen atoms to
 20 which they are attached, which ring is unsubstituted
 or substituted with Z_1 , Z_2 and Z_3 ;

Z_{11} and Z_{12} are each independently:

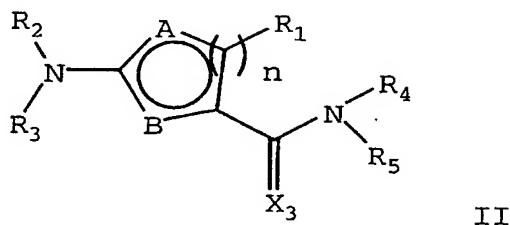
- (1) a single bond;
- (2) alkylene;
- 25 (3) alkenylene; or
- (4) alkynylene; and

Z_{13} is:

- (1) a single bond;
- (2) $-Z_{11}-S(O)_q-Z_{12}-$;
- 30 (3) $-Z_{11}-C(O)-Z_{12}-$;
- (4) $-Z_{11}-C(S)-Z_{12}-$;

- (5) $-Z_{11}-O-Z_{12}-$;
 (6) $-Z_{11}-S-Z_{12}-$;
 (7) $-Z_{11}-O-C(O)-Z_{12}-$;
 (8) $-Z_{11}-C(O)-O-Z_{12}-$;
 5 (9) $-C(NR_{13})-$;
 (10) $-C(CHR_{14})-$; or
 (11) $-C(C(R_{14})_2)-$.

Compounds within formula I include compounds of the following
 formula II and salts thereof:



where

n is 1 or 2

- 15 A is selected from carbon and nitrogen;
 B is selected from nitrogen, oxygen and sulfur;
 X₃ is oxygen or sulfur; and
 R₁, R₂, R₃, R₄ and R₅ are as described above.

20

Detailed Description of the Invention

The following are definitions of terms used in this specification.

- The initial definition provided for a group or term herein applies to that
 group or term throughout the present specification, individually or as part
 25 of another group, unless otherwise indicated.

The terms "alk" or "alkyl" refer to straight or branched chain
 hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8 carbon

atoms. The expression "lower alkyl" refers to alkyl groups of 1 to 4 carbon atoms.

The term "alkenyl" refers to straight or branched chain hydrocarbon groups of 2 to 10, preferably 2 to 4, carbon atoms having at least one
5 double bond. Where an alkenyl group is bonded to a nitrogen atom, it is preferred that such group not be bonded directly through a carbon bearing a double bond.

The term "alkynyl" refers to straight or branched chain hydrocarbon groups of 2 to 10, preferably 2 to 4, carbon atoms having at
10 least one triple bond. Where an alkynyl group is bonded to a nitrogen atom, it is preferred that such group not be bonded directly through a carbon bearing a triple bond.

The term "alkylene" refers to a straight chain bridge of 1 to 5 carbon atoms connected by single bonds (e.g., $-(CH_2)_x-$ wherein x is 1 to 5),
15 which may be substituted with 1 to 3 lower alkyl groups.

The term "alkenylene" refers to a straight chain bridge of 2 to 5 carbon atoms having one or two double bonds that is connected by single bonds and may be substituted with 1 to 3 lower alkyl groups. Exemplary alkenylene groups are $-CH=CH-CH=CH-$, $-CH_2-CH=CH-$,
20 $-CH_2-CH=CH-CH_2-$, $-C(CH_3)_2CH=CH-$ and $-CH(C_2H_5)-CH=CH-$.

The term "alkynylene" refers to a straight chain bridge of 2 to 5 carbon atoms that has a triple bond therein, is connected by single bonds, and may be substituted with 1 to 3 lower alkyl groups. Exemplary alkynylene groups are $-C\equiv C-$, $-CH_2-C\equiv C-$, $-CH(CH_3)-C\equiv C-$ and
25 $-C\equiv C-CH(C_2H_5)CH_2-$.

The terms "ar" or "aryl" refer to aromatic cyclic groups (for example 6 membered monocyclic, 10 membered bicyclic or 14 membered tricyclic ring systems) which contain 6 to 14 carbon atoms. Exemplary aryl groups include phenyl, naphthyl, biphenyl and anthracene.

30 The terms "cycloalkyl" and "cycloalkenyl" refer to cyclic hydrocarbon groups of 3 to 12 carbon atoms.

The terms "halogen" and "halo" refer to fluorine, chlorine, bromine and iodine.

The term "unsaturated ring" includes partially unsaturated and aromatic rings.

5 The terms "heterocycle", "heterocyclic" or "heterocyclo" refer to fully saturated or unsaturated, including aromatic (i.e. "heteroaryl") cyclic groups, for example, 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring systems, which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of
10 the heterocyclic group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom
15 of the ring or ring system.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl,
20 tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodiny, 2-oxoazepinyl, azepinyl, 4-piperidonyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and
25 tetrahydro-1,1-dioxothienyl, triazolyl, triazinyl, and the like.

Exemplary bicyclic heterocyclic groups include indolyl, benzothiazolyl, benzoxazolyl, benzodioxolyl, benzothienyl, quinuclidinyl, quinolinyl, tetra-hydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl,
30 benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]pyridinyl] or

furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), tetrahydroquinolinyl and the like.

Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, acridinyl, phenanthridinyl, xanthenyl and
5 the like.

The term "heteroaryl" refers to aromatic heterocyclic groups.

Exemplary heteroaryl groups include pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furyl, thienyl, oxadiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl,
10 triazolyl, triazinyl, and the like.

Where q is 1 or 2, " $-C(O)_qH$ " denotes $-C(O)-H$ or $-C(O)-OH$; " $-C(O)_qR_6$ " or " $-C(O)_qZ_6$ " denote, respectively, $-C(O)-R_6$ or $-C(O)-OR_6$, or $-C(O)-Z_6$ or $-C(O)-OZ_6$; " $-O-C(O)_qR_6$ " or " $-O-C(O)_qZ_6$ " denote, respectively, $-O-C(O)-R_6$ or $-O-C(O)-OR_6$, or $-O-C(O)-Z_6$ or $-O-C(O)-OZ_6$; and " $-S(O)_qR_6$ " or " $-S(O)_qZ_6$ "
15 denote, respectively, $-SO-R_6$ or $-SO_2-R_6$, or $-SO-Z_6$ or $-SO_2-Z_6$.

Compounds of the formula I may in some cases form salts which are also within the scope of this invention. Reference to a compound of the formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes
20 acidic and/or basic salts formed with inorganic and/or organic acids and bases. Zwitterions (internal or inner salts) are included within the term "salt(s)" as used herein (and may be formed, for example, where the R substituents comprise an acid moiety such as a carboxyl group). Also included herein are quaternary ammonium salts such as alkylammonium
25 salts. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are useful, for example, in isolation or purification steps which may be employed during preparation. Salts of the compounds of the formula I may be formed, for example, by reacting a compound I with an amount of acid or base, such
30 as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, 5 camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates, methanesulfonates, 2-naphthalenesulfonates, 10 nicotines, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates, undecanoates, and the like.

15 Exemplary basic salts (formed, for example, where the R substituents comprise an acidic moiety such as a carboxyl group) include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) 20 such as benzathines, dicyclohexylamines, hydrabamines, N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. The basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g. methyl, ethyl, propyl, and butyl chlorides, bromides and 25 iodides), dialkyl sulfates (e.g. dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g. decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

Prodrugs and solvates of the compounds of the invention are also 30 contemplated herein. The term "prodrug", as employed herein, denotes a compound which, upon administration to a subject, undergoes chemical

conversion by metabolic or chemical processes to yield a compound of the formula I, or a salt and/or solvate thereof. Solvates of the compounds of formula I are preferably hydrates.

All stereoisomers of the present compounds, such as those which
5... may exist due to asymmetric carbons on the R substituents of the compound of the formula I, including enantiomeric and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as
10 racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations.

Throughout the specification, groups and substituents thereof are chosen to provide stable moieties and compounds.

15

Preferred Compounds

Preferred compounds of the present invention are compounds of the formula I, and salts thereof, wherein Q is thiazole and wherein one or more, and especially all, of Z, X₁, X₂, R₁, R₂, R₃, R₄, and R₅ are selected from
20 the following definitions:

Z is a single bond;

R₁ is selected from hydrogen, halo, alkyl, aryl, alkoxy, alkoxycarbonyl, or aryloxycarbonyl and is more preferably hydrogen;

X₁ and X₂ together form =O or =S and more preferably form =O;

25 R₂ is hydrogen;

R₃ is selected from -Z₄-R₆ or -Z₁₃-NR₇R₈ and is more preferably -Z₄-R₆ wherein Z₄ is a single bond and R₆ is aryl or heteroaryl which is unsubstituted or substituted with Z₁, Z₂ and one or more (preferably, one or two) groups Z₃;

30 R₄ is hydrogen; and

R_5 is selected from aryl groups or heteroaryl groups which are substituted with Z_1 , Z_2 and one or more (such as one or two) groups Z_3 .

Methods of Preparation

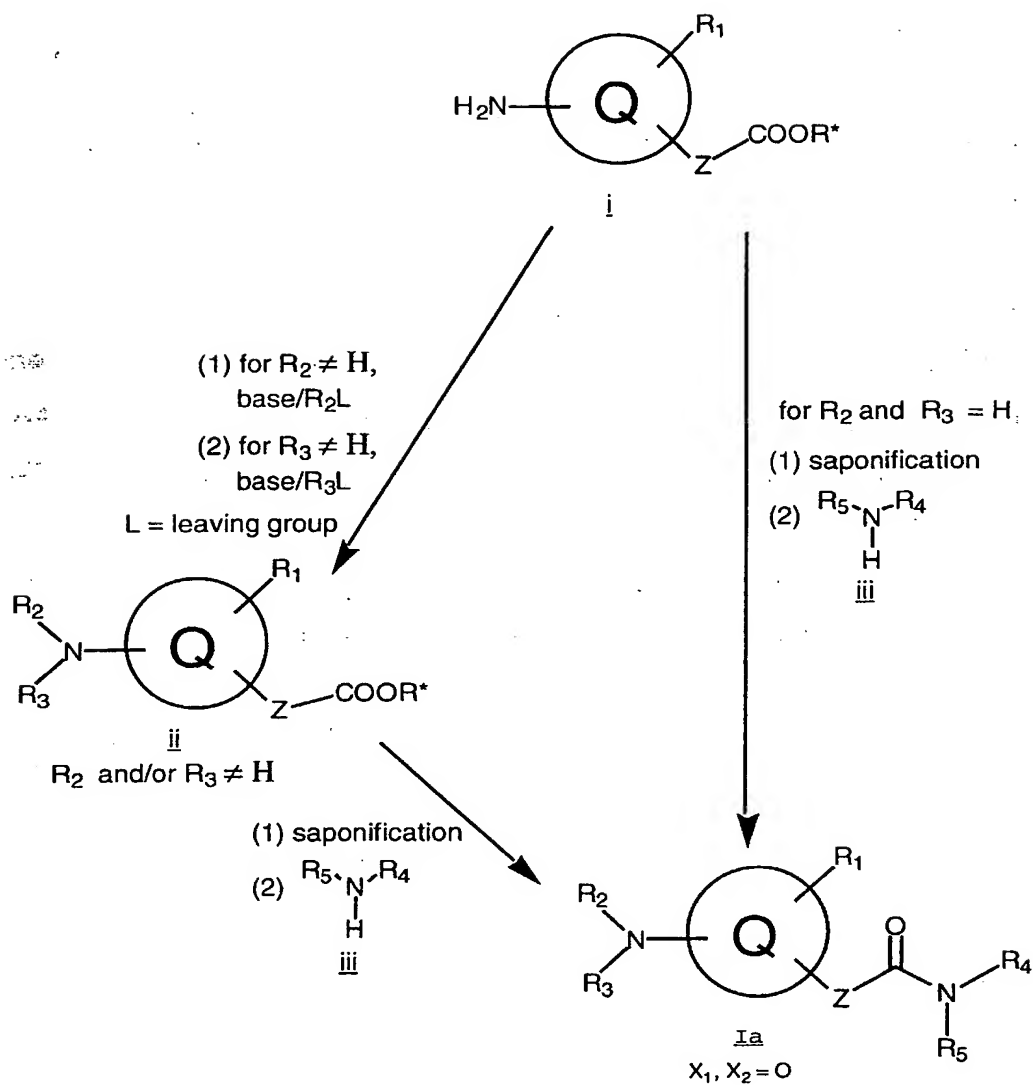
- 5 The compounds of the formula I may be prepared by methods such as those illustrated in the following Schemes A through E and I through XI. Solvents, temperatures, pressures, and other reaction conditions may readily be selected by one of ordinary skill in the art. All documents cited are incorporated herein by reference in their entirety.
- 10 Starting materials are commercially available or readily prepared by one of ordinary skill in the art. Constituents of compounds are as defined elsewhere in the specification or as specifically defined in a scheme.

 The methods described herein may be carried out with starting materials and/or reagents in solution or alternatively, where appropriate,

15 with one or more starting materials or reagents bound to a solid support (see (1) Thompson, L. A., Ellman, J. A., *Chemical Reviews*, 96, 555-600 (1996); (2) Terrett, N. K., Gardner, M., Gordon, D. W., Kobylecki, R. J., Steele, J., *Tetrahedron*, 51, 8135-8173 (1995); (3) Gallop, M. A., Barrett, R. W., Dower, W. J., Fodor, S. P. A., Gordon, E. M., *Journal of Medicinal*

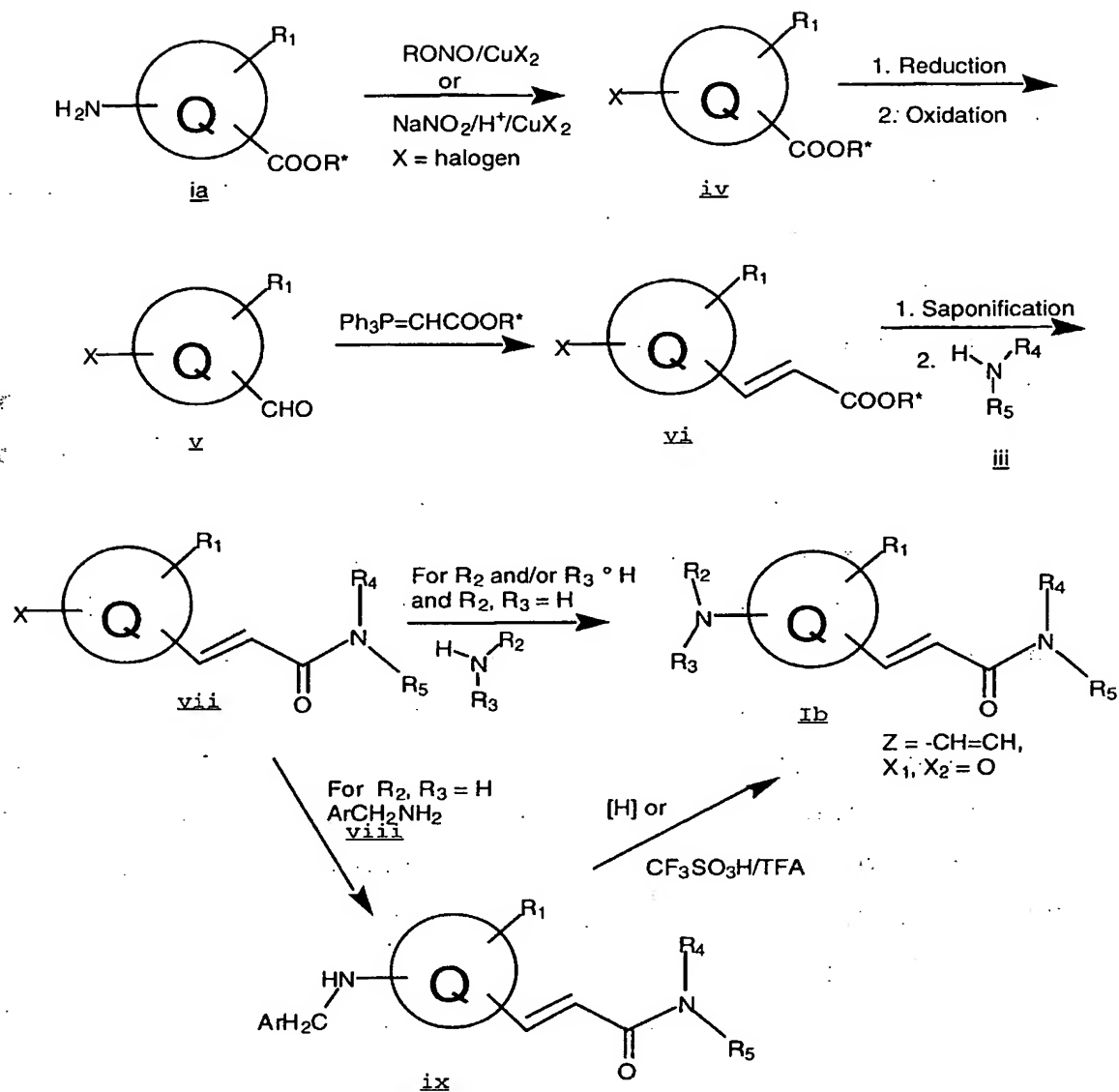
20 *Chemistry*, 37, 1233-1251 (1994); (4) Gordon, E. M., Barrett, R. W., Dower, W. J., Fodor, S. P. A., Gallop, M. A., *Journal of Medicinal Chemistry*, 37, 1385-1401 (1994); (5) Balkenhohl, F., von dem Bussche-Hünnefeld, Lansky, A., Zechel, C., *Angewandte Chemie International Edition in English*, 35, 2288-2337 (1996); (6) Balkenhohl, F., von dem Bussche-

25 Hünnefeld, Lansky, A., Zechel, C., *Angewandte Chemie*, 108, 2436-2487 (1996); and (7) Sofia, M. J., *Drugs Discovery Today*, 1, 27-34 (1996)).

Scheme A

Scheme A illustrates a general method for forming compound Ia, which is a compound of the formula I where X_1 and X_2 together form $=O$. As shown in Scheme A, compound Ia where R_2 and R_3 are hydrogen may be formed by saponification of i, (R^* is a carboxyl protecting group such as alkyl or arylalkyl) followed by reaction with amine iii by methods known in the art. Alternatively i may be reacted with R_2L , where L is a leaving group such as halogen (for example, in equimolar portions), optionally followed by reaction with R_3L (for example, in equimolar portions) to form ii. Also alternatively, i may be subjected to reductive amination using the appropriate aldehyde or ketone to form ii. The compound ii may then be saponified and reacted with amine iii, under conditions known to those skilled in the art, to form Ia where R_2 and/or R_3 are other than hydrogen.

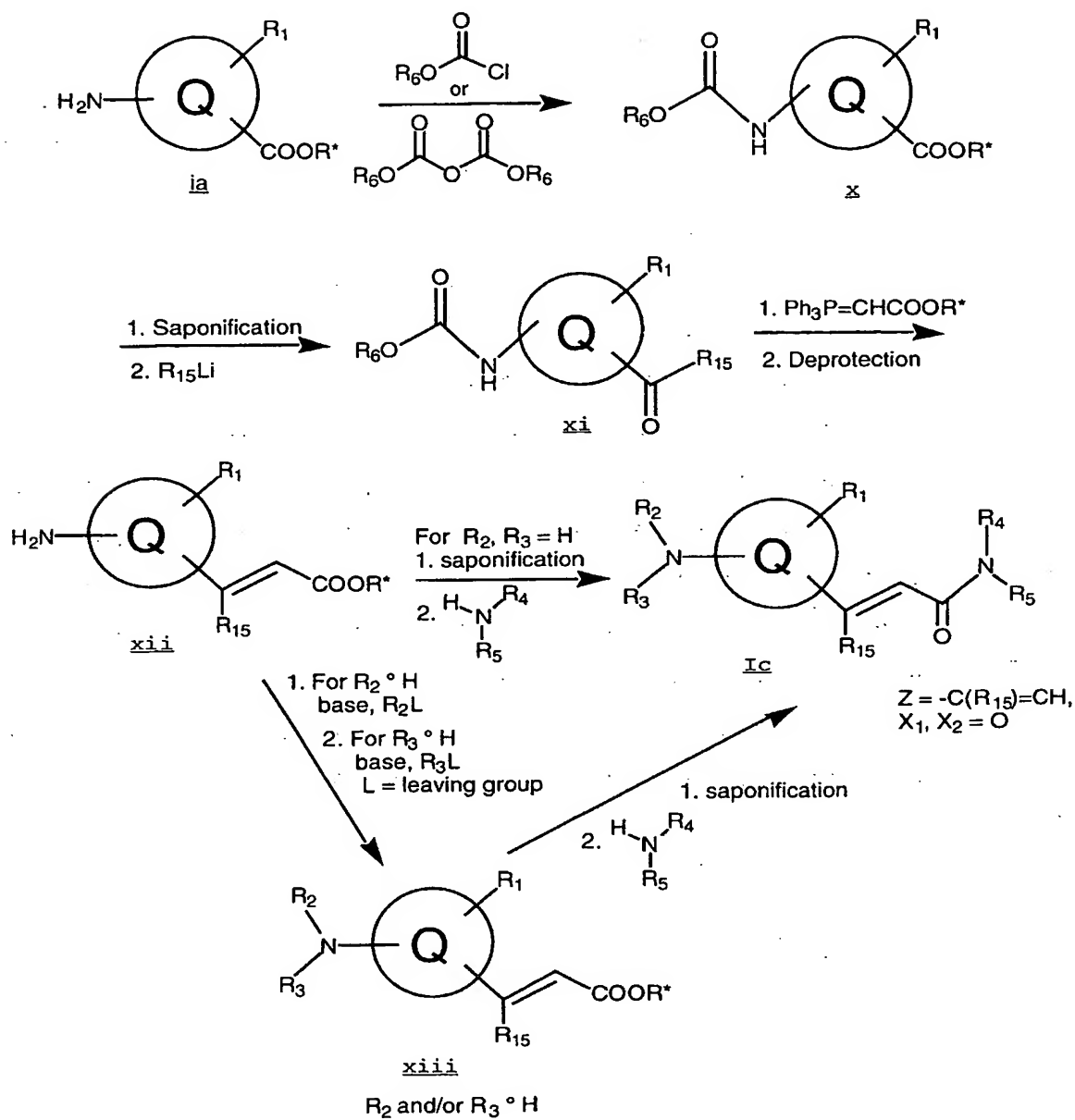
Methods for preparing preferred substituents on the compounds I are illustrated in the following Schemes I to XI.

Scheme B

Scheme B illustrates a general method for forming compound Ib, which is a compound of formula I where Z is -CH=CH- and X₁ and X₂ together form =O. As shown in Scheme B, a 2-halo-compound vi can be prepared by reacting an appropriately substituted 2-amino-compound ia with copper (ii) halide and an alkyl nitrite such as tert-butyl nitrite in an aprotic solvent such as acetonitrile to form 2-halo-compound iv (see *J. Het. Chem.* 22, 1621 (1985)). Compound iv can be reduced with a reducing agent such as sodium borohydride in ethanol or aqueous tetrahydrofuran to form an alcohol, which can be oxidized with an oxidizing agent such as pyridinium chlorochromate or pyridinium dichromate to form aldehyde v. Compound v can be reacted with an alkyl(triphenylphosphorylidene) acetate to form carboxylate vi. Compound vi can be saponified and then reacted with an amine iii by methods known to those skilled in the art to form vii. Compound vii can be reacted with an amine R₂R₃NH to form Ib where Z is -CH=CH- and X₁, X₂ together form =O. Alternatively, compounds of formula Ib where R₂ and R₃ are H, can be formed by reacting compound vii with an appropriately substituted benzyl amine such as 4-methoxybenzyl amine to form compound ix, which can be hydrogenolyzed or treated with an acid such as trifluoromethanesulfonic acid and trifluoroacetic acid in the presence of anisole to form Ib where R₂ and R₃ are hydrogen.

Methods for preparing preferred substituents on the compounds I are illustrated in the following Schemes I to XI.

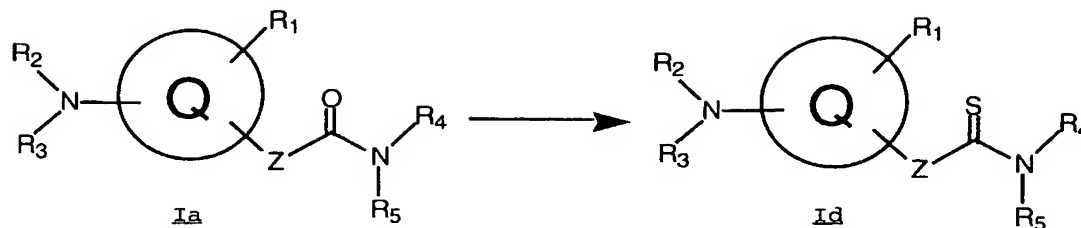
Scheme C



Scheme C illustrates a general method for forming compound Ic, which is a compound of formula I where Z is $-R_{15}C=CH-$ and X_1 and X_2 together form $=O$. As shown in Scheme C, a 2-amino-compound ia can be
5 reacted with a chloroformate or dicarbonate to form x, which can be saponified and treated with an organolithium reagent to form compound xi. Compound xi may be reacted with an alkyl(triphenylphosphorylidene)acetate, followed by deprotection of the carbamate protecting group to form xii. Alternatively,
10 compound Ic where R_2 and R_3 are hydrogen may be formed by saponification of xii followed by reaction with an amine R_4R_5NH by methods known to those skilled in the art. Alternatively, compound xii may be reacted with R_2L where L is a leaving group such as halogen (for example, in equimolar portions), optionally followed by reaction with R_3L
15 (for example, in equimolar portions) to form xiii, which may be saponified and reacted with an amine R_4R_5NH by methods known to those skilled in the art to form Ia where R_2 and/or R_3 are other than hydrogen.

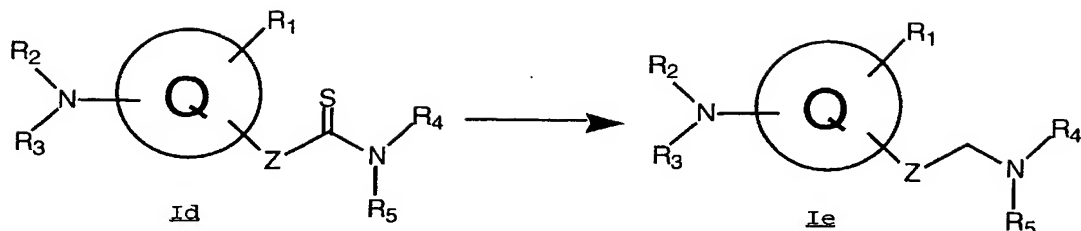
Methods for preparing preferred substituents on the compounds I are illustrated in the following Schemes I to XI.

20

Scheme D

- 5 Scheme D illustrates a general method for forming compound Id, which is a compound of the formula I where X_1 and X_2 together form =S. The compounds of the formula Ia obtained in Scheme A may be converted into the corresponding thioamide Id using a reagent such as Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-
- 10 disulfide (see *Bull. Soc. Chim. Belg.*, 87, 223 (1978)).

Methods for preparing preferred substituents on the compounds I are illustrated in the following Schemes I to XI.

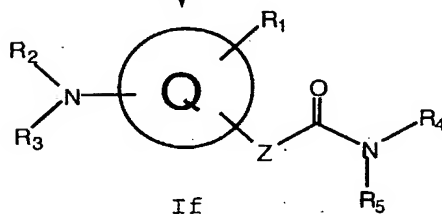
Scheme E

5 Scheme E illustrates a general method for forming compound Ie, which is a compound of the formula I where X₁ and X₂ are each hydrogen. As shown in Scheme E, the compound of the formula Id obtained in Scheme D may be converted into the corresponding amine Ie by reduction, for example, by reaction with Raney nickel.

10 Methods for preparing preferred substituents on the compounds I are illustrated in the following Schemes I to XI.

$$\begin{array}{c}
 \text{H}_2\text{N}-\text{Q}-\text{R}_1 \\
 | \\
 \text{Z}-\text{COOR}^*
 \end{array}
 \xrightarrow[\left(\text{R}_6\text{O}-\text{C}(=\text{O})\right)_2\text{O}]{\text{R}_6\text{O}-\text{C}(=\text{O})\text{Cl} \text{ or }}
 \begin{array}{c}
 \text{H}-\text{N}-\text{Q}-\text{R}_1 \\
 | \quad | \\
 \text{R}_3 \quad \text{R}_6
 \end{array}
 \xrightarrow[\text{KOH}]{\begin{array}{l} (1) \text{ Base/R}_2\text{X} \\ \text{X = halogen} \\ \text{for R}_2 = \text{alkyl, arylalkyl} \\ \text{or cycloalkylalkyl} \end{array}}
 \begin{array}{c}
 \text{R}_2-\text{N}-\text{Q}-\text{R}_1 \\
 | \quad | \\
 \text{R}_3 \quad \text{Z}-\text{COOH}
 \end{array}
 \xrightarrow{\text{KOH}}
 \begin{array}{c}
 \text{H}-\text{N}-\text{Q}-\text{R}_1 \\
 | \quad | \\
 \text{R}_3 \quad \text{Z}-\text{COOH}
 \end{array}$$

OR

$$(2) \begin{array}{c} R^5 - N - R^4 \\ | \\ H \end{array}$$


$R_3 = \text{COOR}_6$
 $X_1, X_2 = \text{O}$
 starting from 2: $R_2 = \text{alkyl, arylalkyl}$
 or cycloalkylalkyl
 starting from 3: $R_2 = \text{H}$

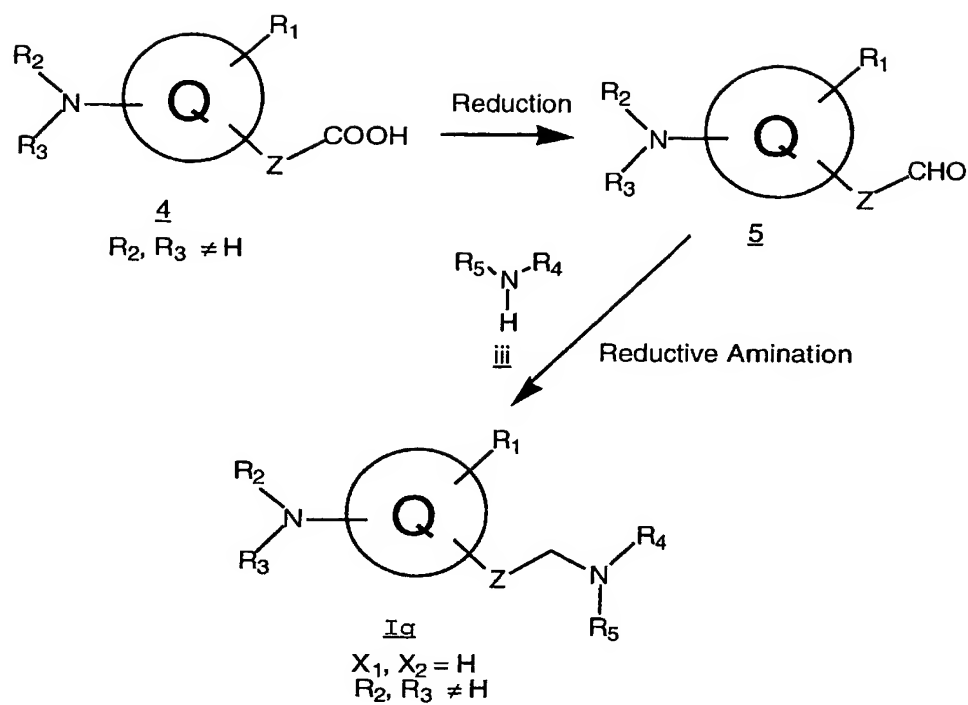
As shown in Scheme I, carboxylate i can be reacted with a chloroformate or dicarbonate to form 1. Compound 1 can be treated with a base such as sodium hydride, sodium/potassium hexamethyldisilazide, or lithium diisopropylamide (LDA), and an alkylating agent R_2X where X is halogen and R_2 is preferably alkyl, arylalkyl, or cycloalkylalkyl, and then saponified with an aqueous base such as potassium hydroxide to give 2. Alternatively, 1 can be subjected to reductive amination using the appropriate aldehyde or ketone and saponified with an aqueous base such as potassium hydroxide to give 2. Compound 1 may, alternatively, be simply saponified with an aqueous base such as potassium hydroxide to give 3 where R_2 is hydrogen.

Acid 2 may be reacted with an amine iii using reaction conditions well known in the art for peptide bond synthesis (see, for example, Bodanszky and Bodanszky, *The Practice of Peptide Chemistry*, Springer-Verlag, 1984; Bodanszky, *Principles of Peptide Synthesis*, Springer-Verlag, 1984) to give the compound Id which is a compound of the formula I where X_1 and X_2 together form $=O$, R_3 is $COOR_6$, and, since 2 is the starting material, R_2 is preferably alkyl, arylalkyl or cycloalkylalkyl. For example, reagents which activate the carboxyl group of 2 for reaction with the amine iv include bis-(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP chloride), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent), [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium] hexafluorophosphate (HATU), and carbodiimides such as dicyclohexylcarbodiimide (DCC) or 3-ethyl-3'-(dimethylamino)propylcarbodiimide (EDCI) either alone or in combination with a hydroxybenzotriazole. Alternatively, the activated ester intermediate can be isolated and then treated with the appropriate amine iv in a nonprotic solvent such as tetrahydrofuran (THF) or dimethylformamide (DMF) in the presence of a base, for example, an organic base such as sodium/potassium hexamethyldisilazide, triethylamine, diisopropylethylamine or 1,8-diazabicyclo[5.4.0]undec-7-

ene (DBU), or an inorganic base such as sodium, potassium or cesium carbonate or sodium or potassium hydride. Alternatively, the acid halide of 2 may be prepared, for example, by reaction with thionyl chloride or oxalyl chloride, followed by subsequent reaction with amine iii to provide
5 compound If, which is a compound of the formula I where R_3 is COOR_6 , X_1 and X_2 together form $=\text{O}$, and R_2 is alkyl, arylalkyl or chycloalkylalkyl.

Similar reactions as employed above for the conversion of 2 to If may be used to convert 3 to If where R_3 is COOR_6 , X_1 and X_2 together form $=\text{O}$, and R_2 is hydrogen.

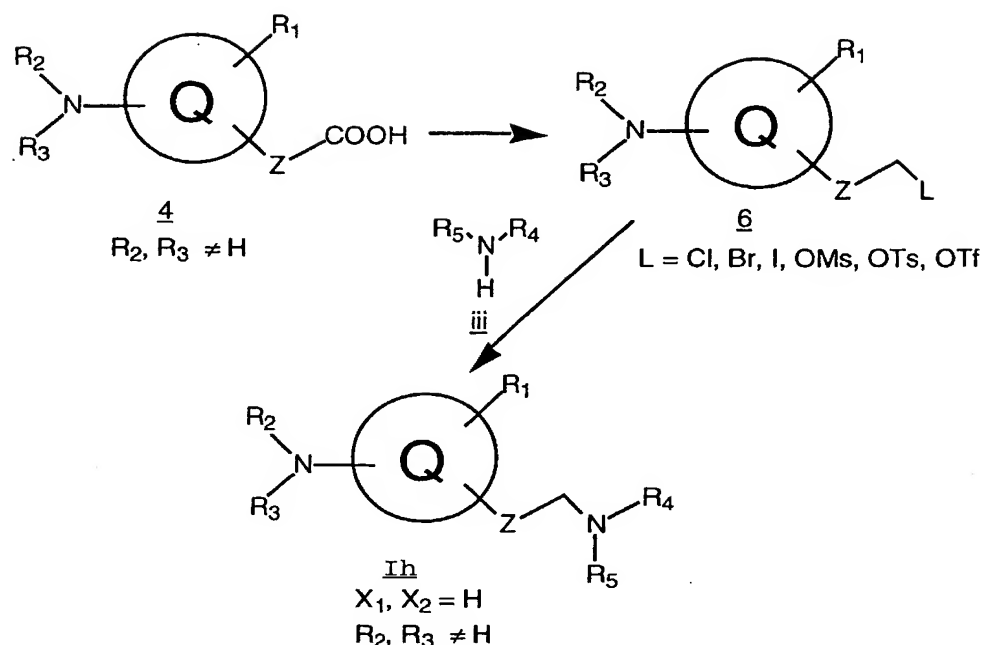
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Scheme II

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As shown in Scheme II, acid 4 where R_2 and R_3 are not hydrogen and are selected such that the nitrogen to which they are attached is non-basic, is reduced to the aldehyde 5 by methods well known in the art (see March, Advanced Organic Chemistry, Wiley, 1985). For example, the acid 4 may be converted to its corresponding ester followed by reduction with diisobutylaluminum hydride. Alternatively, the acid 4 may be reduced to the corresponding primary alcohol, for example, by treatment with borane/THF, $LiAlH_4$, or via reduction of a mixed anhydride, followed by subsequent oxidation to the aldehyde 5 using Cr(VI) (e.g., pyridinium chlorochromate, "PCC") or under Swern or Moffatt conditions (e.g., $(COCl)_2$ /dimethylsulfoxide). The starting acid 4 may be obtained, for example, by saponification of ii.

Reductive amination (see Hudlicky, Reductions in Organic Chemistry, Wiley, 1984) of aldehyde 5 with amine iii in the presence of a reducing agent such as $NaBH_3CN$, $NaBH(OAc)_3$ (Ac = acetyl) or hydrogen and a palladium catalyst produces the amine compound Ig, which is a compound of the formula I where X_1 and X_2 are each hydrogen and R_2 and R_3 are each not hydrogen.

Scheme III

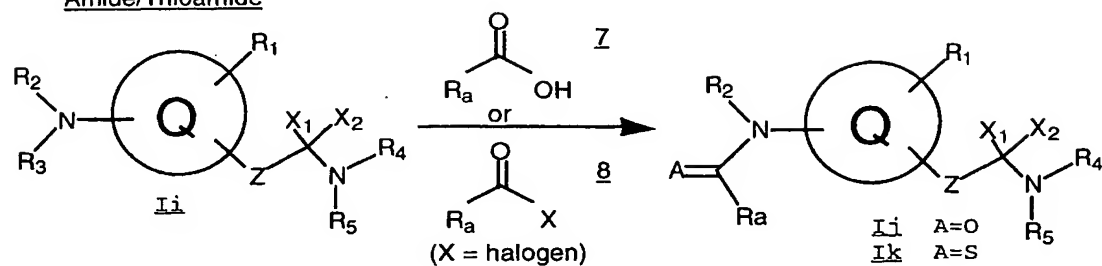
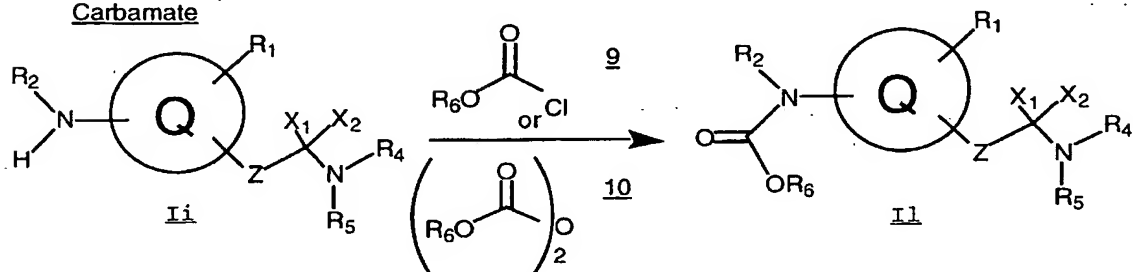
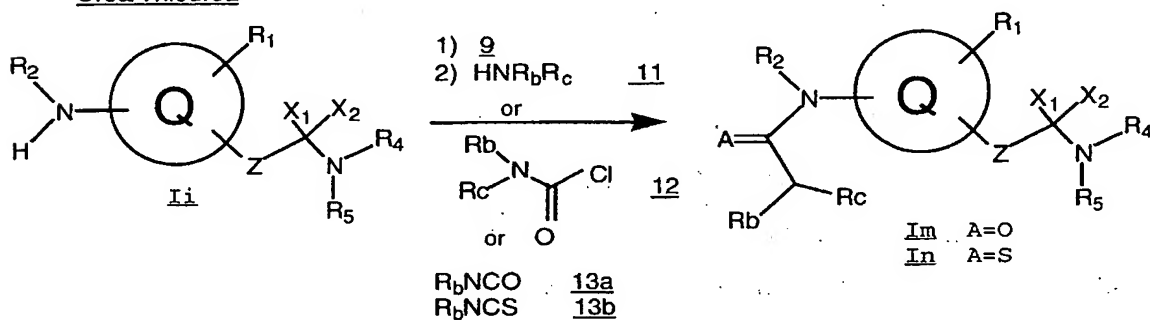
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As shown in Scheme III, reduction of the acid 4 to a primary alcohol (for example, by treatment with borane/tetrahydrofuran, LiAlH_4 , or via reduction of a mixed anhydride), followed by conversion by methods well known in the art (see March, Advanced Organic Chemistry, Wiley, 1985), provides 6 which contains a leaving group such as a halide, tosylate (OTs), mesylate (OMs) or triflate (OTf). The groups R_2 and R_3 are selected such that the resulting nitrogen to which they are attached is non-basic.

Compound 6 can then be converted into compound Ih, which is a compound of the formula I where X_1 and X_2 are each hydrogen and R_2 and R_3 are each not hydrogen, by a displacement reaction with amine iii, preferably where amine iii is used in excess.

Scheme IV

R_2 = any group as defined
 R_3 = acyl or thioacyl

Amide/ThioamideCarbamateUrea/Thiourea

$[X_1, X_2 \neq \text{H}]$

Scheme IV illustrates methods which may be used for the preparation of compounds Ij, Ik, Il, Im and In. Ij, Ik, Il, Im and In are compounds of the formula I where R_2 is any group as defined, R_3 is an acyl or thioacyl group, X_1 and X_2 are not hydrogen, and R_1 is not a primary or secondary amine. Ij, Ik, Il, Im and In have other particular substituents which are specified in this Scheme and below. The starting compound Ii can be prepared by suitable methods described in Schemes A and D.

Amide Ij can be prepared by treatment of amine compound Ii with a carboxylic acid 7 in the presence of reagents which activate the carboxyl group for reaction as described above, for example BOP reagent, HATU, and carbodiimides such as DCC or EDCI either alone or in combination with a hydroxybenztriazole. Alternatively, the acid halide 8 may be reacted with amine compound Ii in the presence of an acid scavenger such as diisopropylethylamine. The corresponding thioamide Ik can be prepared by the treatment of amide Ii (where $X_1, X_2 \neq O$) with Lawesson's reagent as described above.

Carbamate Il can be prepared by treatment of amine compound Ii with a chloroformate 9 or dicarbonate 10 in the presence of an acid scavenger such as diisopropylethylamine.

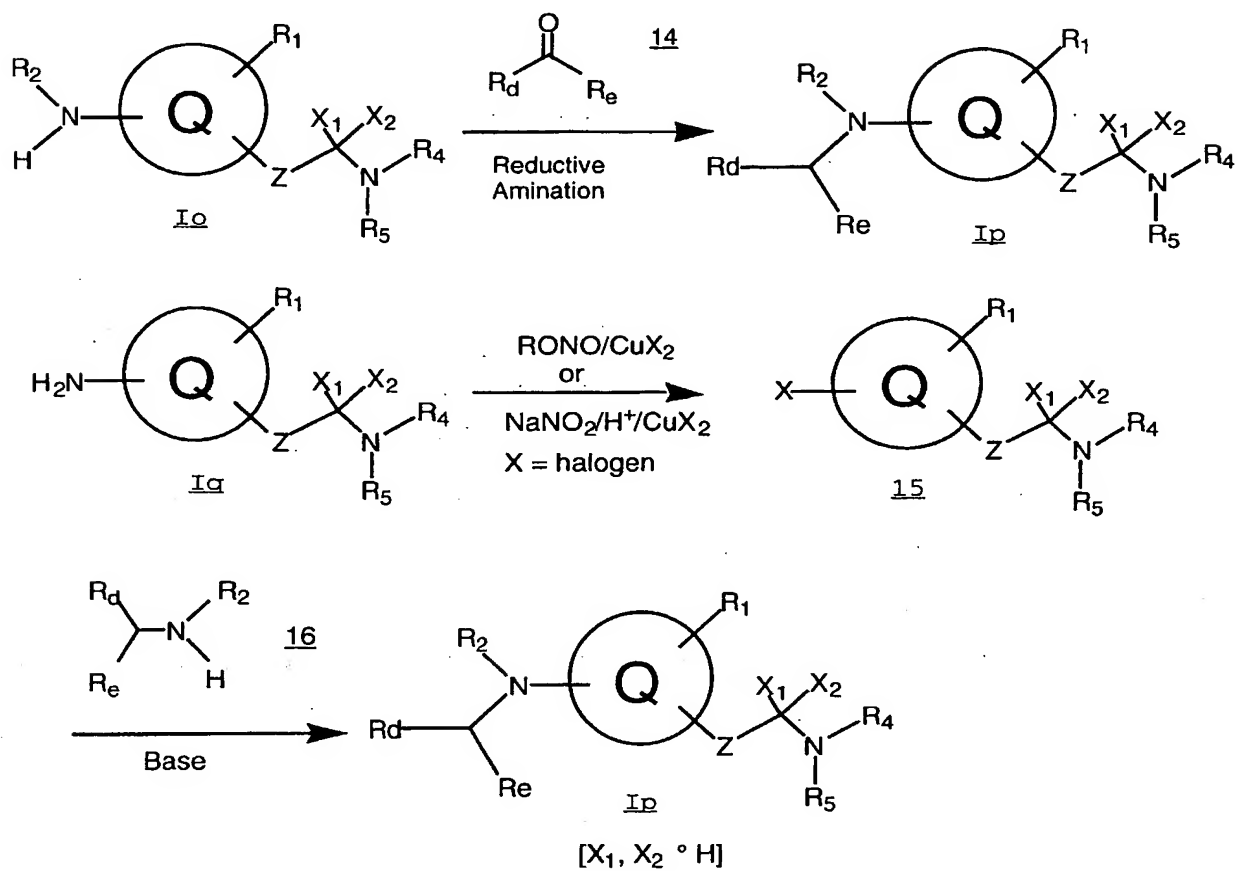
The urea Im may be prepared by treatment of amine compound Ii with either: 1) a chloroformate 9, such as phenylchloroformate, followed by reaction with an amine 11; 2) a carbamoyl chloride 12 in the presence of an acid scavenger such as diisopropylethylamine; or 3) reaction with an isocyanate 13a (where R_c in Im = H). The corresponding thiourea In may be prepared by treatment of amine compound Ii with a thioisocyanate 13b.

R_a is selected from those groups included in the definition of R_6 such that the group $-C(=A)-R_a$ is an acyl or thioacyl group within the definition of R_3 . R_b and R_c are selected from those groups included in the definitions of R_7 and R_8 , such that the group $-C(=A)-N(R_b)(R_c)$ is an acyl or thioacyl group within the definition of R_3 .

Scheme V

R_2 = any group as defined other than acyl

R_3 = alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aralkyl or saturated heterocycle



Scheme V illustrates a method which can be used for the preparation of Ip, which is a compound of the formula I where R₂ is any group as defined other than acyl, and which is selected such that the nitrogen to which it is attached is basic, R₃ is alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aralkyl, or saturated heterocycle, and X₁ and X₂ are not hydrogen. The starting compounds Io and Iq can be prepared by suitable methods described in Schemes A and D.

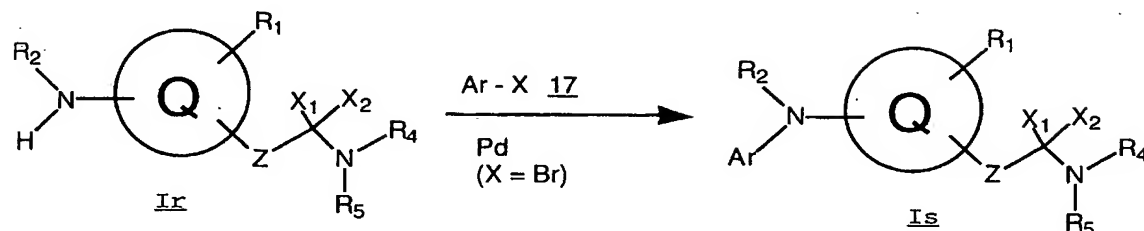
As shown in Scheme V, amine compound Io is reacted with an aldehyde or ketone 14 under reductive amination conditions described above to give the amine Ip. Compound Ip may also be prepared by treatment of an amine compound Iq, where R₂ and R₃ are hydrogen, with t-butyl nitrite or sodium nitrite in the presence of a copper (II) halide to give the halo-substituted compound 15, followed by displacement with amine 16 in the presence of a base such as sodium or potassium hydride or the like (see Lee et al., *J. Heterocyclic Chemistry*, 22, 1621 (1985)).

R_d and R_e are independently selected from hydrogen, alkyl, aryl, cycloalkyl or cycloalkenyl, or together are alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring, such that the group -CH(R_d)(R_e) is a group within the definition of R₃.

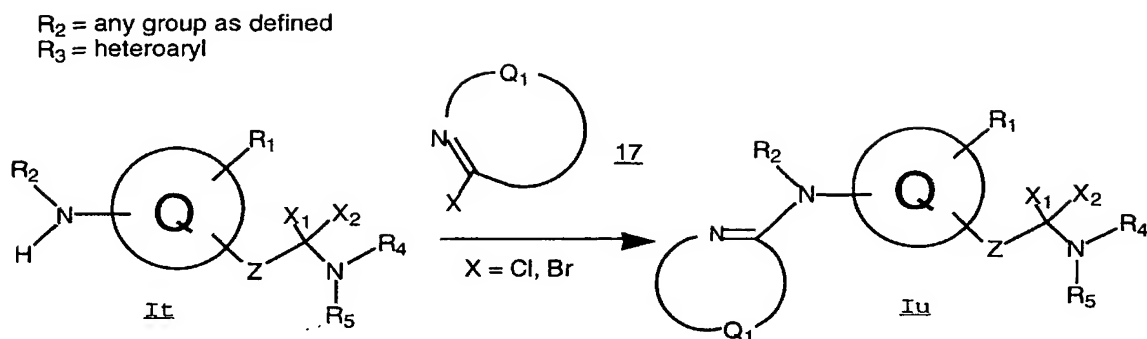
Scheme VI

R_2 = any group as defined other than acyl

R_3 = aryl, heteroaryl



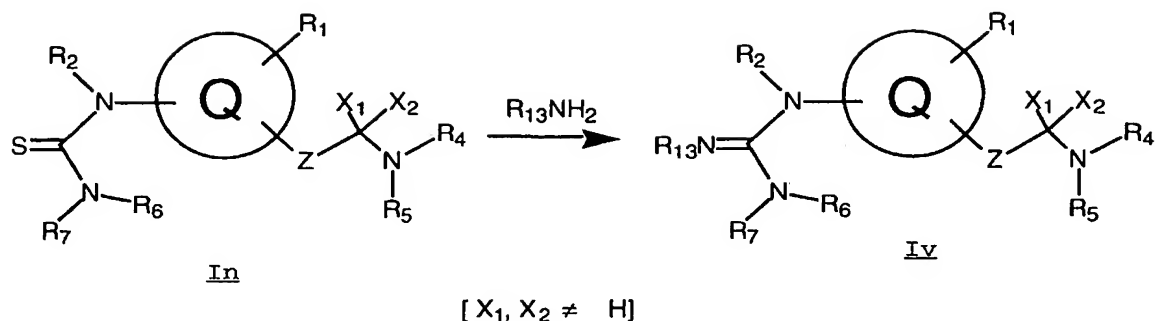
As shown in Scheme VI, when R_2 is any group as defined other than acyl, and is selected such that the nitrogen to which it is attached is basic, R_3 is aryl or heteroaryl, and X_1 and X_2 are not hydrogen, amine compound **Ir** may be reacted with a halophenyl or haloheteroaromatic group **17** in the presence of a palladium (0) catalyst (see *J. Am. Chem. Soc.*, 118, 7215 (1996)) to give amine **Is**, which is a compound of the formula I having the particular substituents described in this Scheme. The starting compound **Ir** can be prepared by suitable methods described in Schemes A and D.

Scheme VII

5

- As shown in Scheme VII, when R_2 is any group as defined and R_3 is a heteroaromatic group, amine compound It may be reacted, in the presence of a base if needed, with a 2-halosubstituted heteroaromatic compound 17 where Q_1 , together with atoms to which it is bonded, forms a 5- or 6-membered monocyclic or 10- to 12-membered bicyclic heteroaromatic group (such as forming 2-chloropyridine or 2-chloropyrimidine) to give the amine Iu, where Iu is a compound of the formula I having the particular substituents described in this Scheme.
- The starting compound It can be prepared by suitable methods described in Schemes A and D.

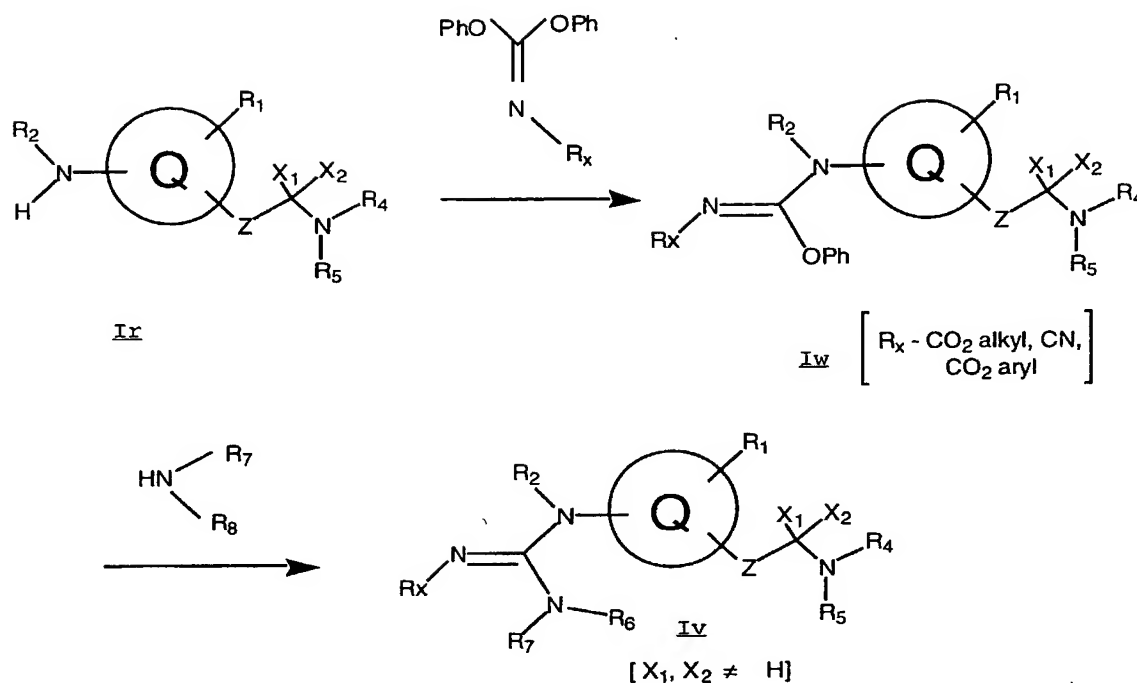
Scheme VIII



As shown in Scheme VIII, thiourea compound In (where X_1 and X_2 are not hydrogen) may be reacted with the appropriate amine in the presence of bis-(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP chloride) benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP-reagent), [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium]hexafluorophosphate (HATU) and carbodiimide, such as dicyclohexyl carbodiimide (DCC) or 3-ethyl-3'-(dimethylamino)propyl carbodiimide (EDCI) or diisopropyl carbodiimide (DIC) in the presence of an organic base such as triethylamine, diisopropylethylamine or dimethylaminopyridine in solvents such as dimethylformamide, dichloromethane or tetrahydrofuran to form compound Iv, which is a compound of the formula I having the particular substituents described in this Scheme.

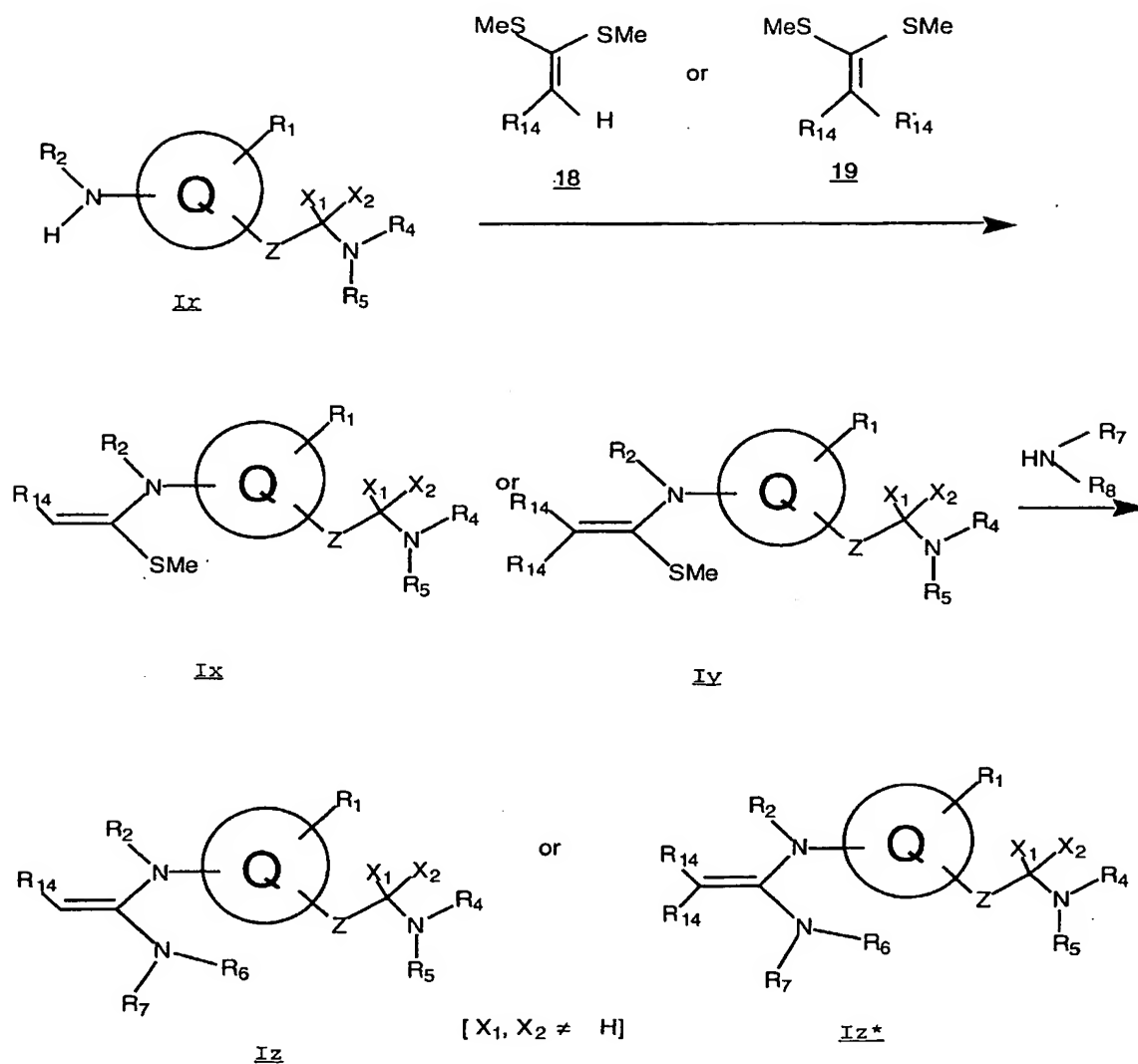
Alternatively, Compound In can be reacted with the appropriate amine in the presence of a mercury (II) salt such as mercuric chloride, or by other methods known in the literature, to form Iv.

Scheme IX



- As shown in Scheme IX, amine **Ir** (where X_1 and X_2 are not hydrogen)
- 5 can be reacted with diphenylcyanocarbonimidate either alone or in the presence of a base such as sodium hydride, sodium hexamethyldisilazide or dimethylaminopyridine in acetonitrile, tetrahydrofuran, or dimethylformamide at room temperature or elevated temperature to form intermediate compound **Iw**. Compound **Iw** can be reacted with an amine
- 10 $\text{R}_7\text{R}_8\text{NH}$ to form compound **Iv**, which is a compound of the formula I having the particular substituents described in this Scheme.

Scheme X

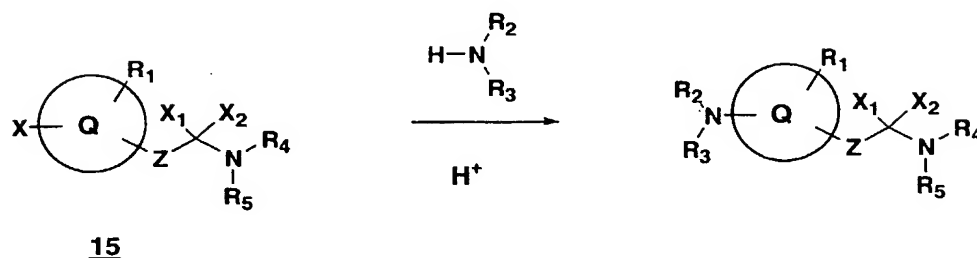


As shown in Scheme X, compound **Ir** (where X_1 and X_2 are not hydrogen) can be reacted with **18** or **19** either alone or in the presence of a base such as sodium hydride, sodium hexamethyl disilazide or dimethylaminopyridine in dimethyl formamide or tetrahydrofuran at room temperature or at higher temperature to form compounds **Ix** or **Iy** respectively, which can be reacted with an amine R_7R_8NH at room temperature or elevated temperature to form compounds **Iz** or **Iz***

respectively. Compound Iz is a compound of the formula I having the particular substituents described in this Scheme. Compound Iz* is a compound of the formula I having the particular substituents described in this Scheme.

Scheme XI

R_2 = aryl, heteroaryl, bicyclic-heteroaryl
 R_3 = H, alkyl, aryl, heteroaryl, bicyclic-heteroaryl



5 As shown in Scheme XI, compounds of formula I can also be prepared from 15 by treatment with the defined amine in the presence of an acid catalyst (for example, see: Gunzenhauser et al., *Helv. Chim. Acta*, 71, 33 (1988)).

10 Utility

The compounds of the present invention inhibit protein tyrosine kinases, especially Src-family kinases such as Lck, Fyn, Lyn, Src, Yes, Hck, Fgr and Blk, and are thus useful in the treatment, including prevention and therapy, of protein tyrosine kinase-associated disorders such as immunologic and oncologic disorders. The compounds inhibit also receptor tyrosine kinases including HER1 and HER2 and are therefore useful in the treatment of proliferative disorders such as psoriasis and cancer. The ability of these compounds to inhibit HER1 and other receptor kinases will also permit their use as anti-angiogenic agents to treat disorders such as cancer and diabetic retinopathy. "Protein tyrosine kinase-associated disorders" are those disorders which result from aberrant tyrosine kinase activity, and/or which are alleviated by the inhibition of one or more of these enzymes. For example, Lck inhibitors are of value in the treatment of a number of such disorders (for example, the treatment of autoimmune diseases), as Lck inhibition blocks T cell

activation. The treatment of T cell mediated diseases, including inhibition of T cell activation and proliferation, is a particularly preferred embodiment of the present invention. Compounds which selectively block T cell activation and proliferation are preferred. Compounds of the present invention which block the activation of endothelial cell PTK by oxidative stress, thereby limiting surface expression of adhesion molecules that induce neutrophil binding, and which inhibit PTK necessary for neutrophil activation are useful, for example, in the treatment of ischemia and reperfusion injury.

10 The present invention thus provides methods for the treatment of protein tyrosine kinase-associated disorders, comprising the step of administering to a subject in need thereof at least one compound of the formula I in an amount effective therefor. Other therapeutic agents such as those described below may be employed with the inventive compounds in the present methods. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with or following the administration of the compound(s) of the present invention.

20 Use of the compounds of the present invention in treating protein tyrosine kinase-associated disorders is exemplified by, but is not limited to, treating a range of disorders such as: transplant (such as organ transplant, acute transplant or heterograft or homograft (such as is employed in burn treatment)) rejection; protection from ischemic or reperfusion injury such as ischemic or reperfusion injury incurred during organ transplantation, myocardial infarction, stroke or other causes; 25 transplantation tolerance induction; arthritis (such as rheumatoid arthritis, psoriatic arthritis or osteoarthritis); multiple sclerosis; chronic obstructive pulmonary disease (COPD), such as emphysema; inflammatory bowel disease, including ulcerative colitis and Crohn's 30 disease; lupus (systemic lupus erythematosus); graft vs. host disease; T-cell mediated hypersensitivity diseases, including contact hypersensitivity,

delayed-type hypersensitivity, and gluten-sensitive enteropathy (Celiac disease); psoriasis; contact dermatitis (including that due to poison ivy); Hashimoto's thyroiditis; Sjogren's syndrome; Autoimmune Hyperthyroidism, such as Graves' Disease; Addison's disease

5 (autoimmune disease of the adrenal glands); Autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome); autoimmune alopecia; pernicious anemia; vitiligo; autoimmune hypopituitarism; Guillain-Barre syndrome; other autoimmune diseases; cancers, including cancers where Lck or other Src-family kinases such as
10 Src are activated or overexpressed, such as colon carcinoma and thymoma, and cancers where Src-family kinase activity facilitates tumor growth or survival; glomerulonephritis; serum sickness; urticaria; allergic diseases such as respiratory allergies (asthma, hayfever, allergic rhinitis) or skin allergies; scleroderma; mycosis fungoides; acute inflammatory responses
15 (such as acute respiratory distress syndrome and ischemia/reperfusion injury); dermatomyositis; alopecia areata; chronic actinic dermatitis; eczema; Behcet's disease; Pustulosis palmoplanteris; Pyoderma gangrenum; Sezary's syndrome; atopic dermatitis; systemic sclerosis; and morphea. The present invention also provides a method for treating
20 the aforementioned disorders such as atopic dermatitis by administration of any compound capable of inhibiting protein tyrosine kinase.

Src-family kinases other than Lck, such as Hck and Fgr, are important in the Fc gamma receptor responses of monocytes and macrophages. Compounds of the present invention inhibit the Fc gamma
25 dependent production of TNF alpha in the monocyte cell line THP-1 that does not express Lck. The ability to inhibit Fc gamma receptor dependent monocyte and macrophage responses results in additional anti-inflammatory activity for the present compounds beyond their effects on T cells. This activity is especially of value, for example, in the treatment of
30 inflammatory diseases such as arthritis or inflammatory bowel disease. In particular, the present compounds are of value for the treatment of

autoimmune glomerulonephritis and other instances of glomerulonephritis induced by deposition of immune complexes in the kidney that trigger Fc gamma receptor responses leading to kidney damage.

5 In addition, Src family kinases other than Lck, such as Lyn and Src, are important in the Fc epsilon receptor induced degranulation of mast cells and basophils that plays an important role in asthma, allergic rhinitis, and other allergic disease. Fc epsilon receptors are stimulated by IgE-antigen complexes. Compounds of the present invention inhibit the
10 Fc epsilon induced degranulation responses, including in the basophil cell line RBL that does not express Lck. The ability to inhibit Fc epsilon receptor dependent mast cell and basophil responses results in additional anti-inflammatory activity for the present compounds beyond their effect on T cells. In particular, the present compounds are of value for the
15 treatment of asthma, allergic rhinitis, and other instances of allergic disease.

The combined activity of the present compounds towards monocytes, macrophages, T cells, etc. may be of value in the treatment of any of the aforementioned disorders.

20 In a particular embodiment, the compounds of the present invention are useful for the treatment of the aforementioned exemplary disorders irrespective of their etiology, for example, for the treatment of transplant rejection, rheumatoid arthritis, multiple sclerosis, chronic obstructive pulmonary disease, inflammatory bowel disease, lupus, graft
25 v. host disease, T-cell mediated hypersensitivity disease, psoriasis, Hashimoto's thyroiditis, Guillain-Barre syndrome, cancer, contact dermatitis, allergic disease such as allergic rhinitis, asthma, ischemic or reperfusion injury, or atopic dermatitis whether or not associated with PTK.

30 By virtue of their ability to inhibit HER1 and HER2 kinases, compounds of the present invention can also be used for the treatment of

proliferative diseases, including psoriasis and cancer. The HER1 receptor kinase has been shown to be expressed and activated in many solid tumors including non-small cell lung, colorectal, and breast cancer. Similarly, the HER2 receptor kinase has been shown to be overexpressed

5 in breast, ovarian, lung and gastric cancer. Monoclonal antibodies that downregulate the abundance of the HER2 receptor or inhibit signaling by the HER1 receptor have shown anti-tumor efficacy in preclinical and clinical studies. It is therefore expected that inhibitors of the HER1 and HER2 kinases will have efficacy in the treatment of tumors that depend

10 on signaling from either of the two receptors. These compounds are expected to have efficacy either as single agent or in combination with other chemotherapeutic agents such as paclitaxel (Taxol), doxorubicin hydrochloride (adriamycin), and cisplatin (Platinol). See the following documents and references cited therein: Cobleigh, M. A., Vogel, C. L.,

15 Tripathy, D., Robert, N. J., Scholl, S., Fehrenbacher, L., Wolter, J. M., Paton, V., Shak, S., Lieberman, G., and Slamon, D. J., "Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease", J.

20 of Clin. Oncol. 17(9), p. 2639-2648 (1999); Baselga, J., Pfister, D., Cooper, M. R., Cohen, R., Burtness, B., Bos, M., D'Andrea, G., Seidman, A., Norton, L., Gunnett, K., Falcey, J., Anderson, V., Waksal, H., and Mendelsohn, J., "Phase I studies of anti-epidermal growth factor receptor chimeric antibody C225 alone and in combination with cisplatin", J. Clin.

25 Oncol. 18(4), p. 904-914 (2000).

The present invention also provides pharmaceutical compositions comprising at least one of the compounds of the formula I capable of treating a protein tyrosine kinase-associated disorder in an amount effective therefor, and a pharmaceutically acceptable vehicle or diluent.

30 The compositions of the present invention may contain other therapeutic agents as described below, and may be formulated, for example, by

employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known
5 in the art of pharmaceutical formulation.

The compounds of the formula I may be administered by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection
10 or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents. The present compounds
15 may, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic
20 pumps. The present compounds may also be administered liposomally.

Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring
25 agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The present compounds may also be delivered
30 through the oral cavity by sublingual and/or buccal administration. Molded tablets, compressed tablets or freeze-dried tablets are exemplary

forms which may be used. Exemplary compositions include those formulating the present compound(s) with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses
5 (avicel) or polyethylene glycols (PEG). Such formulations may also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g., Carbopol
10 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

Exemplary compositions for nasal aerosol or inhalation administration include solutions in saline which may contain, for example, benzyl alcohol or other suitable preservatives, absorption
15 promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as
20 mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

Exemplary compositions for rectal administration include
25 suppositories which may contain, for example, a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the drug.

Exemplary compositions for topical administration include a
30 topical carrier such as Plastibase (mineral oil gelled with polyethylene).

The effective amount of a compound of the present invention may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for an adult human of from about 0.1 to 100 mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. It will be understood that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats and the like, subject to protein tyrosine kinase-associated disorders.

The compounds of the present invention may be employed alone or in combination with each other and/or other suitable therapeutic agents useful in the treatment of protein tyrosine kinase-associated disorders such as PTK inhibitors other than those of the present invention, antiinflammatories, antiproliferatives, chemotherapeutic agents, immunosuppressants, anticancer agents and cytotoxic agents.

Exemplary such other therapeutic agents include the following: cyclosporins (e.g., cyclosporin A), CTLA4-Ig, antibodies such as anti-ICAM-3, anti-IL-2 receptor (Anti-Tac), anti-CD45RB, anti-CD2, anti-CD3 (OKT-3), anti-CD4, anti-CD80, anti-CD86, monoclonal antibody OKT3, agents blocking the interaction between CD40 and gp39, such as antibodies specific for CD40 and/or gp39 (i.e., CD154), fusion proteins constructed from CD40 and gp39 (CD40Ig and CD8gp39), inhibitors, such as nuclear translocation inhibitors, of NF-kappa B function, such as deoxyspergualin (DSG), non-steroidal antiinflammatory drugs (NSAIDs) such as ibuprofen, steroids such as prednisone or dexamethasone, gold

compounds, antiproliferative agents such as methotrexate, FK506 (tacrolimus, Prograf), mycophenolate mofetil, cytotoxic drugs such as azathioprine and cyclophosphamide, TNF- α inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor such as etanercept (Enbrel),
5 rapamycin (sirolimus or Rapamune), leflunimide (Arava), and cyclooxygenase-2 (COX-2) inhibitors such as celecoxib (Celebrex) and rofecoxib (Vioxx), or derivatives thereof, and the PTK inhibitors disclosed in the following U.S. Patent Applications, incorporated herein by reference in their entirety: Serial No. 60/056,770, filed 8/25/97 (Attorney Docket No.
10 QA202*), Serial No. 60/069,159, filed 12/9/97 (Attorney Docket No. QA202a*), Serial No. 09/097,338, filed 6/15/98 (Attorney Docket No. QA202b), Serial No. 60/056,797, filed 8/25/97 (Attorney Docket No. QA205*), Serial No. 09/094,797, filed 6/15/98 (Attorney Docket No. QA205a), Serial No. 60/065,042, filed 11/10/97 (Attorney Docket No.
15 QA207*), Serial No. 09/173,413, filed 10/15/98, (Attorney Docket No. QA207a), Serial No. 60,076,789, filed 3/4/98 (Attorney Docket No. QA208*), and Serial No. 09,262,525, filed 3/4/99 (Attorney Docket No. QA208a). See the following documents and references cited therein: Hollenbaugh, D., Douthwright, J., McDonald, V., and Aruffo, A.,
20 "Cleavable CD40Ig fusion proteins and the binding to sgp39", *J. Immunol. Methods* (Netherlands), 188(1), p. 1-7 (Dec 15 1995); Hollenbaugh, D., Grosmaire, L.S., Kullas, C.D., Chalupny, N.J., Braesch-Andersen, S., Noelle, R.J., Stamenkovic, I., Ledbetter, J.A., and Aruffo, A., "The human T cell antigen gp39, a member of the TNF gene family, is a ligand for the
25 CD40 receptor: expression of a soluble form of gp39 with B cell co-stimulatory activity", *EMBO J* (England), 11(12), p 4313-4321 (Dec 1992); and Moreland, L.W. et al., "Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein, *New England J. of Medicine*, 337(3), p. 141-147 (1997).
30 Exemplary classes of anti-cancer agents and cytotoxic agents include, but are not limited to: alkylating agents, such as nitrogen

mustards, alkyl sulfonates, nitrosoureas, ethylenimines, and triazenes; antimetabolites, such as folate antagonists, purine analogues, and pyrimidine analogues; antibiotics, such as anthracyclines, bleomycins, mitomycin, dactinomycin, and plicamycin; enzymes, such as L-asparaginase; farnesyl-protein transferase inhibitors; hormonal agents, such as glucocorticoids, estrogens/antiestrogens, androgens/antiandrogens, progestins, and luteinizing hormone-releasing hormone antagonists, octreotide acetate; microtubule-disruptor agents, such as ecteinascidins or their analogs and derivatives; microtubule-stabilizing agents such as paclitaxel (Taxol®), docetaxel (Taxotere®), and epothilones A-F or their analogs or derivatives; plant-derived products, such as vinca alkaloids, epipodophyllotoxins, taxanes; and topoisomerase inhibitors; prenyl-protein transferase inhibitors; and miscellaneous agents such as, hydroxyurea, procarbazine, mitotane, hexamethylmelamine, platinum coordination complexes such as cisplatin and carboplatin; and other agents used as anti-cancer and cytotoxic agents such as biological response modifiers, growth factors; immune modulators, and monoclonal antibodies. The compounds of the invention may also be used in conjunction with radiation therapy.

Representative examples of these classes of anti-cancer and cytotoxic agents include, but are not limited to, mechlorethamine hydrochloride, cyclophosphamide, chlorambucil, melphalan, ifosfamide, busulfan, carmustine, lomustine, semustine, streptozocin, thiotepa, dacarbazine, methotrexate, thioguanine, mercaptopurine, fludarabine, pentastatin, cladribin, cytarabine, fluorouracil, doxorubicin hydrochloride, daunorubicin, idarubicin, bleomycin sulfate, mitomycin C, actinomycin D, safracins, saframycins, quinocarcins, discodermolides, vincristine, vinblastine, vinorelbine tartrate, etoposide, teniposide, paclitaxel, tamoxifen, estramustine,

estramustine phosphate sodium, flutamide, buserelin, leuprolide, pteridines, diynes, levamisole, aflacon, interferon, interleukins, aldesleukin, filgrastim, sargramostim, rituximab, BCG, tretinoin, irinotecan hydrochloride, betamethosone, gemcitabine hydrochloride, 5 altretamine, and topoteca and any analogs or derivatives thereof.

Preferred members of these classes include, but are not limited to paclitaxel, cisplatin, carboplatin, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, mitomycin C, ecteinascidin 743, porfiromycin, 5-fluorouracil, 6-mercaptopurine, 10 gemcitabine, cytosine arabinoside, podophyllotoxin or podophyllotoxin derivatives such as etoposide, etoposide phosphate or teniposide, melphalan, vinblastine, vincristine, leurosine, vindesine, and leurosine.

Examples of anti-cancer and other cytotoxic agents include the 15 following: epothilone derivatives as found in U.S. Serial No. 09/506,481 filed February 17, 2000 (Attorney Docket No. LD186); German Patent No. 4138042.8; WO 97/19086, WO 98/22461, WO 98/25929, WO 98/38192, WO 99/01124, WO 99/02224, WO 99/02514, WO 99/03848, WO 99/07692, WO 99/27890, WO 20 99/28324, WO 99/43653, WO 99/54330, WO 99/54318, WO 99/54319, WO 99/65913, WO 99/67252, WO 99/67253, and WO 00/00485; cyclin dependent kinase inhibitors as found in WO 99/24416; and prenyl-protein transferase inhibitors as found in WO 97/30992 and WO 98/54966.

25 The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

The following assays can be employed in ascertaining the degree 30 of activity of a compound ("test compound") as a PTK inhibitor.

Compounds described in the following Examples have been tested in one or more of these assays, and have shown activity.

Enzyme Assay Using Lck, Fyn, Lyn, Hck, Fgr, Src, Blk or Yes

5 The following assay has been carried out using the protein tyrosine kinases *Lck, Fyn, Lyn, Hck, Fgr, Src, Blk and Yes*.

 The protein tyrosine kinase of interest is incubated in kinase buffer (20 mM MOPS, pH7, 10 mM MgCl₂) in the presence of the test compound. The reaction is initiated by the addition of substrates to the final
10 concentration of 1 μM ATP, 3.3 μCi/ml [33P] gamma-ATP, and 0.1 mg/ml acid denatured enolase (prepared as described in Cooper, J.A., Esch, F.S., Taylor, S.S., and Hunter, T., "Phosphorylation sites in enolase and lactate dehydrogenase utilized by tyrosine protein kinases in vivo and in vitro", *J. Biol. Chem.*, 259, 7835-7841 (1984)). The reaction is stopped after 10
15 minutes by the addition of 10% trichloroacetic acid, 100 mM sodium pyrophosphate followed by 2 mg/ml bovine serum albumin. The labeled enolase protein substrate is precipitated at 4 degrees, harvested onto Packard Unifilter plates and counted in a Topcount scintillation counter to ascertain the protein tyrosine kinase inhibitory activity of the test
20 compound (activity inversely proportional to the amount of labeled enolase protein obtained). The exact concentration of reagents and the amount of label can be varied as needed.

 This assay is advantageous as it employs an exogenous substrate (enolase) for more accurate enzyme kinetics, and can be conducted in a 96-
25 well format that is readily automated. In addition, His-tagged protein tyrosine kinases (described below) offer much higher production yields and purity relative to GST-protein tyrosine kinase fusion protein.

 The protein tyrosine kinase may be obtained from commercial sources or by recombinant methods described herewith. For the
30 preparation of recombinant Lck, human Lck was prepared as a His-tagged fusion protein using the Life Technologies (Gibco) baculovirus vector

pFastBac Hta (commercially available) in insect cells. A cDNA encoding human Lck isolated by PCR (polymerase chain reaction) was inserted into the vector and the protein was expressed using the methods described by the manufacturer. The Lck was purified by affinity chromatography. For the production of Lck in insect cells using baculovirus, see Spana, C., O'Rourke, E.C., Bolen, J.B., and Fargnoli, J., "Analysis of the tyrosine kinase p56lck expressed as a glutathione S-transferase protein in *Spodoptera frugiperda* cells," *Protein expression and purification*, Vol. 4, p. 390-397 (1993). Similar methods may be used for the recombinant production of other Src-family kinases.

Enzyme Assay Using HER1 or HER2

Compounds of interest were assayed in a kinase buffer that contained 20 mM Tris.HCl, pH 7.5, 10 mM MnCl₂, 0.5 mM dithiothreitol, bovine serum albumin at 0.1 mg/ml, poly(glu/tyr, 4:1) at 0.1 mg/ml, 1 μM ATP, and 4 μCi/ml [gamma-³³P]ATP. Poly(glu/tyr, 4:1) is a synthetic polymer that serves as a phosphoryl acceptor and is purchased from Sigma Chemicals. The kinase reaction is initiated by the addition of enzyme and the reaction mixtures were incubated at 26°C for 1 h. The reaction is terminated by the addition of EDTA to 50 mM and proteins are precipitated by the addition of trichloroacetic acid to 5%. The precipitated proteins are recovered by filtration onto Packard Unifilter plates and the amount of radioactivity incorporated is measured in a Topcount scintillation counter.

For the preparation of recombinant HER1, the cytoplasmic sequence of the receptor were expressed in insect cells as a GST fusion protein, which was purified by affinity chromatography as described above for Lck. The cytoplasmic sequence of HER2 was subcloned into the baculovirus expression vector pBlueBac4 (Invitrogen) and was expressed as an untagged protein in insect cells. The recombinant protein was partially purified by ion-exchange chromatography.

Cell assays(1) Cellular tyrosine phosphorylation

Jurkat T cells are incubated with the test compound and then stimulated by the addition of antibody to CD3 (monoclonal antibody G19-4). Cells are lysed after 4 minutes or at another desired time by the addition of a lysis buffer containing NP-40 detergent. Phosphorylation of proteins is detected by anti-phosphotyrosine immunoblotting. Detection of phosphorylation of specific proteins of interest such as ZAP-70 is detected by immunoprecipitation with anti-ZAP-70 antibody followed by anti-phosphotyrosine immunoblotting. Such procedures are described in Schieven, G.L., Mittler, R.S., Nadler, S.G., Kirihaara, J.M., Bolen, J.B., Kanner, S.B., and Ledbetter, J.A., "ZAP-70 tyrosine kinase, CD45 and T cell receptor involvement in UV and H₂O₂ induced T cell signal transduction", *J. Biol. Chem.*, 269, 20718-20726 (1994), and the references incorporated therein. The Lck inhibitors inhibit the tyrosine phosphorylation of cellular proteins induced by anti-CD3 antibodies.

For the preparation of G19-4, see Hansen, J.A., Martin, P.J., Beatty, P.G., Clark, E.A., and Ledbetter, J.A., "Human T lymphocyte cell surface molecules defined by the workshop monoclonal antibodies," in *Leukocyte Typing I*, A. Bernard, J. Boumsell, J. Dausett, C. Milstein, and S. Schlossman, eds. (New York: Springer Verlag), p. 195-212 (1984); and Ledbetter, J.A., June, C.H., Rabinovitch, P.S., Grossman, A., Tsu, T.T., and Imboden, J.B., "Signal transduction through CD4 receptors: stimulatory vs. inhibitory activity is regulated by CD4 proximity to the CD3/T cell receptor", *Eur. J. Immunol.*, 18, 525 (1988).

(2) Calcium assay

Lck inhibitors block calcium mobilization in T cells stimulated with anti-CD3 antibodies. Cells are loaded with the calcium indicator dye indo-1, treated with anti-CD3 antibody such as the monoclonal antibody G19-4, and calcium mobilization is measured using flow cytometry by recording

changes in the blue/violet indo-1 ratio as described in Schieven, G.L., Mittler, R.S., Nadler, S.G., Kirihaara, J.M., Bolen, J.B., Kanner, S.B., and Ledbetter, J.A., "ZAP-70 tyrosine kinase, CD45 and T cell receptor involvement in UV and H₂O₂ induced T cell signal transduction", *J. Biol. Chem.*, 269, 20718-20726 (1994), and the references incorporated therein.

(3) Proliferation assays

Lck inhibitors inhibit the proliferation of normal human peripheral blood T cells stimulated to grow with anti-CD3 plus anti-CD28 antibodies. A 96 well plate is coated with a monoclonal antibody to CD3 (such as G19-4), the antibody is allowed to bind, and then the plate is washed. The antibody bound to the plate serves to stimulate the cells. Normal human peripheral blood T cells are added to the wells along with test compound plus anti-CD28 antibody to provide co-stimulation. After a desired period of time (e.g., 3 days), the [3H]-thymidine is added to the cells, and after further incubation to allow incorporation of the label into newly synthesized DNA, the cells are harvested and counted in a scintillation counter to measure cell proliferation.

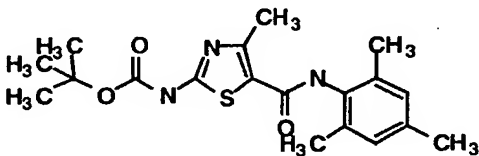
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The following Examples illustrate embodiments of the present invention, and are not intended to limit the scope of the claims. Abbreviations employed in the Examples are defined below. Compounds of the Examples are identified by the example and step in which they are prepared (for example, "1A" denotes the title compound of step A of Example 1), or by the example only where the compound is the title compound of the example (for example, "2" denotes the title compound of Example 2).

25

Abbreviations

- aq. = aqueous
- 5 conc. = concentrated
- DMSO = dimethylsulfoxide
- EtOAc = ethyl acetate
- Et₂O = diethyl ether
- h = hours
- 10 HATU = N-[dimethylamino-1H-1,2,3-triazolo-[4,5-b]pyridin-1-yl
methylene]-N-methyl methanaminium hexafluorophosphate N-
oxide
- MeOH = methanol
- MOPS = 4-morpholine-propanesulfonic acid
- 15 MS = mass spectrometry
- Ret Time = retention time
- RT = room temperature
- satd. = saturated
- TFA = trifluoroacetic acid
- 20 THF = tetrahydrofuran
- DMF = N,N-dimethylformamide

Example 1Preparation of [5-[[[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

5

A. Ethyl-2-tert-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylate

A suspension of ethyl-2-amino-4-methyl-thiazole-5-carboxylate (18.6 g, 100 mmol), di-t-butyldicarbonate (26.2 g, 120 mmol) and 4-dimethylaminopyridine (800 mg, 6.55 mmol) in dry tetrahydrofuran (300 mL) was stirred under nitrogen for 18 h. The solvent was evaporated *in vacuo*. The residue was suspended in dichloromethane (1 L) and filtered through a pad of celite. The filtrate was washed with 1 N aqueous HCl solution (300 mL, 2x), water and brine, dried (MgSO₄), and concentrated *in vacuo*. The residue was triturated with hexanes. The solid was filtered and dried *in vacuo* to obtain the title compound (20 g, 72%) as a tan solid.

B. 2-tert-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylic acid

A stirred solution of ethyl-2-tert-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylate (10 g, 34.95 mmol) in tetrahydrofuran-ethanol (250 mL, 2:3) was treated with a 6N KOH solution (250 mL). The mixture was heated to 55°C overnight. The solution was cooled to 0°C and acidified with concd. HCl to pH 1. The solvent was evaporated *in vacuo*. The residue was washed with water, diethyl ether, dried *in vacuo* over anhydrous phosphorous pentoxide to obtain the title acid (6 g, 89%) as a white solid.

C. 2-tert-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylic acid chloride

A 2 M solution of oxalyl chloride in dichloromethane (22.5 mL, 45 mmol) was added dropwise to a stirred suspension of 2-tert-

- 5 butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylic acid (10 g, 38.72 mmol) in dichloromethane (150 mL) and N,N-dimethyl formamide (150 μ L) at 0°C. The suspension gradually became homogenous after addition was complete. The solution was allowed to warm to room temperature and stirred at rt for 1.5 h. The solvent was evaporated *in vacuo* and the
- 10 residue was coevaporated with toluene (300 mL, 2x) and then dried *in vacuo* to obtain the title acid chloride (10.7 g, 99%) as a tan solid.

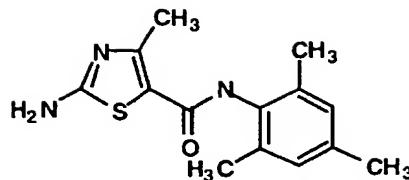
D. [5-[[[(2,4,6-Trimethylphenyl)aminolcarbonyl]-4-methyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

- 15 2,4,6-Trimethyl aniline (6.3 mL, 38.66 mmol) was added dropwise to a stirred solution of 2-tert-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylic acid chloride (10.7 g, 38.66 mmol) in dichloromethane (150 mL) at 0°C. After 20 min, diisopropylethylamine (8.8 mL, 44.88 mmol) was added dropwise. The solution was allowed to warm to rt and stirred for an
- 20 additional 2 h. The solvent was evaporated *in vacuo*. The residue was suspended in EtOAc (700 mL), washed with 1 N aq. HCl solution (300 mL, 2x), water, and brine; dried (MgSO₄), filtered and concentrated. The residue was triturated with ether to obtain the title compound (12.5 g, 86%) as a tan solid.

25

Example 2

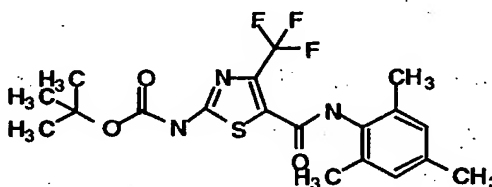
Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-4-methyl-5-thiazolecarboxamide



A solution of [5-[[[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester (10 g, 26.63 mmol) in trifluoroacetic acid (100 mL) was stirred at rt for 3 h. The solution was concentrated under reduced pressure and the residue was diluted with EtOAc (700 mL), washed with 5% aq. KHCO_3 solution (400 mL, 2x), water, and brine; dried (MgSO_4), filtered and concentrated. The residue was washed with ether (200 mL) and acetonitrile (100 mL) to obtain the title compound (6.7 g, 91%) as a white solid.

Example 3

Preparation of [5-[[[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-trifluoromethyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester



A. Ethyl-2-tert-butoxycarbonyloxyamino-4-trifluoromethyl-thiazole-5-carboxylate

A suspension of ethyl-2-amino-4-trifluoromethyl-thiazole-5-carboxylate (5.05 g, 21.02 mmol), di-*t*-butyldicarbonate (4.82 g, 22.07 mmol) and 4-dimethylaminopyridine (260 mg, 2.1 mmol) in dichloromethane (209 mL) was stirred under nitrogen for 1.5 h. The solvent was evaporated *in vacuo*. The residue was chromatographed on a silica gel column. Elution with 5% EtOAc in hexanes, followed by 15% EtOAc in hexanes afforded the title compound (6.57 g, 92%) as a white solid.

B. 2-Tert-butoxycarbonyloxyamino-4-trifluoromethyl-thiazole-5-carboxylic acid

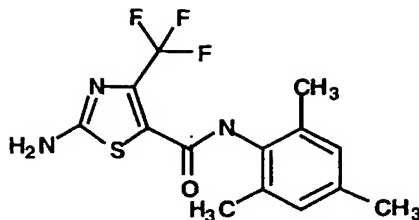
A stirred solution of ethyl-2-*tert*-butoxycarbonyloxyamino-4-trifluoromethyl-thiazole-5-carboxylate (6.5 g, 19.1 mmol) in methanol (100 mL) was treated with a 1N aq. NaOH solution (573 mL). The mixture was stirred at rt overnight. The solution was cooled to 0°C and acidified with a 6 M aq. HCl solution to pH 1 and extracted with chloroform (150 mL, 6x). The chloroform extracts were combined, dried (Na₂SO₄), filtered and concentrated under reduced pressure and *in vacuo* to obtain the title acid (5.75 g, 96%) as a white solid.

C. [5-[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-trifluoromethyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

4-Methylmorpholine (40 µL, 0.39 mmol) was added to a mixture of 2-*tert*-butoxycarbonyloxyamino-4-trifluoromethyl-thiazole-5-carboxylic acid (100 mg, 0.32 mmol), 2,4,6-trimethylaniline (45 µL, 0.32 mmol), and benzotriazol-1-yloxy-tris-(dimethylamino)phosphonium hexafluorophosphate (BOP reagent, 380 mg, 0.4 mmol) in DMF (2 mL). The solution was stirred at rt for 72 h, diluted with dichloromethane and washed with 0.25 M aq. KHSO₄ solution followed by satd. aq. KHCO₃ solution. The dichloromethane extract was separated, dried (Na₂SO₄), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 5% EtOAc in hexanes followed by 10% EtOAc in hexanes to obtain the title compound (90 mg, 65%) as a white solid.

Example 4

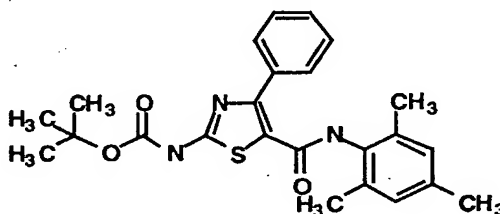
Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-4-trifluoromethyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



A solution of [5-[[[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-trifluoromethyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester (120 mg, 0.28 mmol) in trifluoroacetic acid (5 mL) was stirred at 0°C for 1 h. The solution was concentrated under reduced pressure and the residue was coevaporated with ether to obtain a yellow solid which was triturated with hexanes to obtain the title compound (96 mg, 76%) as a light yellow solid.

Example 5

Preparation of [5-[[[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-phenyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester



A. Ethyl-2-tert-butoxycarbonyloxyamino-4-phenyl-thiazole-5-carboxylate

Compound **5A** was prepared by an analogous method as that of **3A**, except using ethyl-2-amino-4-phenyl-thiazole-5-carboxylate to give the title compound **5A** as a white solid (90.5%).

B. 2-Tert-butoxycarbonyloxyamino-4-phenyl-thiazole-5-carboxylic acid

Compound **5B** was prepared by an analogous method as that of **3B**, except using **5A** to give the title compound **5B** as a white solid (99%).

C. 2-Tert-butoxycarbonyloxycarbonyl-4-phenyl-thiazole-5-carboxylic acid chloride

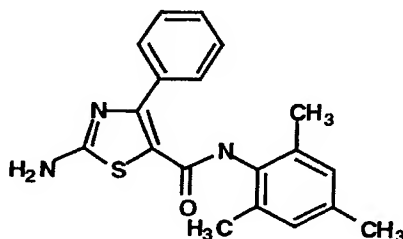
Compound **5C** was prepared by an analogous method as that of **1C**, except
5 using **5B** to give the title compound **5C** as a white solid (90%).

D. [5-[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-phenyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

Compound **5D** was prepared by an analogous method as that of **1D**, except
10 using **5C** to give the title compound **5D** as a light yellow solid (93%).

Example 6

Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-4-phenyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



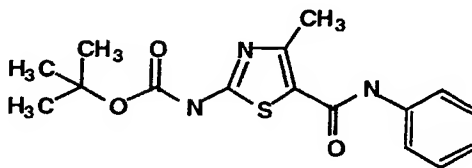
15

Compound **6** was prepared by an analogous method as that of **4**, except
using **5D** to give the title compound **6** as a white solid (68%).

20

Example 7

Preparation of [5-[[Phenylamino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

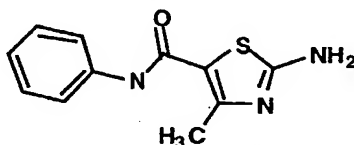


Compound was prepared by an analogous method as that of **1D**, except using aniline in place of 2,4,6-trimethylaniline and triethylamine in place of diisopropylethylamine to give the title compound **7** as an off-white solid (76%).

5

Example 8

Preparation of 2-Amino-N-(phenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)

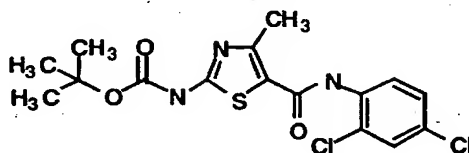


10

Compound **8** was prepared by an analogous method as that of **4**, except using **7** to give the title compound **8** as a white solid (68%).

Example 9

Preparation of [5-[(2,4-Dichlorophenyl)aminolcarbonyl]-4-methyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester



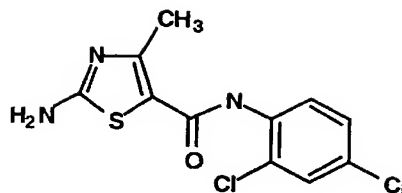
Compound **9** was prepared by an analogous method as that of **1D**, except using 2,4-dichloroaniline to give the title compound **9** as a white solid (28%).

20

Example 10

Preparation of 2-Amino-N-(2,4-dichlorophenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)

25

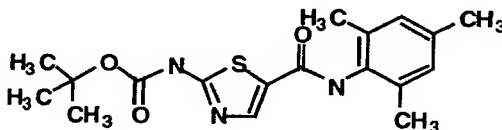


Compound **10** was prepared by an analogous method as that of **4**, except using **9** to give the title compound **8** as a white solid (100%).

5

Example 11

Preparation of 5-[[2,4,6-Trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester



10

A. Ethyl-2-*tert*-butoxycarbonyloxyamino-thiazole-5-carboxylate

Compound **11A** was prepared by an analogous method as that of **3A**, except using ethyl-2-amino-thiazole-5-carboxylate to give the title compound **11A** as a white solid (79.5%).

15

B. 2-*Tert*-butoxycarbonyloxyamino -thiazole-5-carboxylic acid

Compound **11B** was prepared by an analogous method as that of **3B**, except using **11A** to give the title compound **11B** as a white solid (95.5%).

C. 2-*Tert*-butoxycarbonyloxyamino-thiazole-5-carboxylic acid chloride

Compound **11C** was prepared by an analogous method as that of **1C**, except using **11B** to give the title compound **11C**.

D. [5-[[2,4,6-Trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

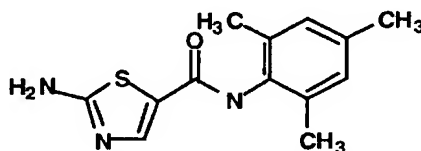
25

Compound **11D** was prepared by an analogous method as that of **1D**, except using **11C** to give the title compound **11D** as an off-white solid (70%).

5

Example 12

Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-4-phenyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



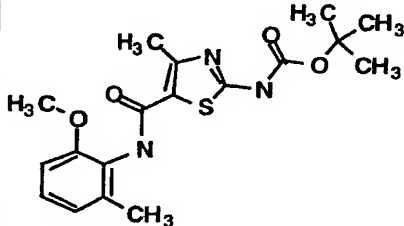
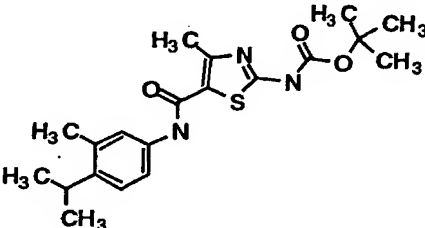
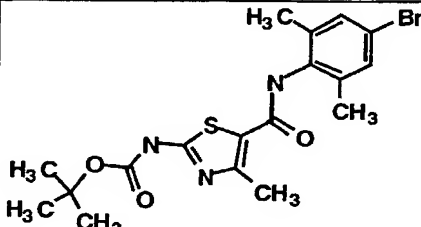
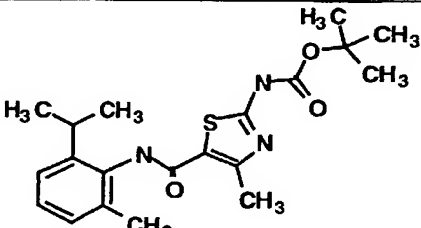
10 Compound **12** was prepared by an analogous method as that of **4**, except using **11D** to give the title compound **12** as a light yellow solid (88%).

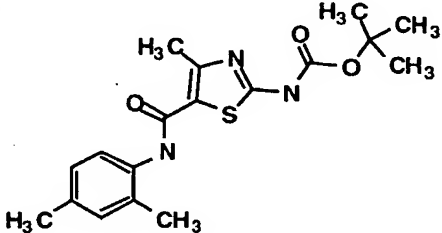
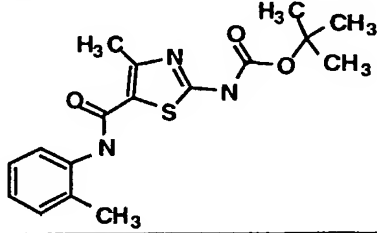
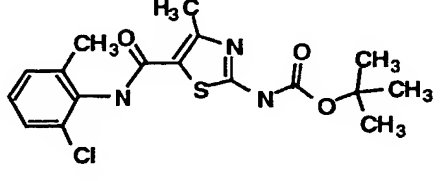
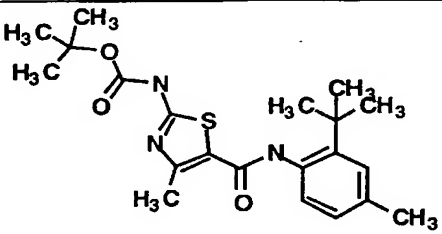
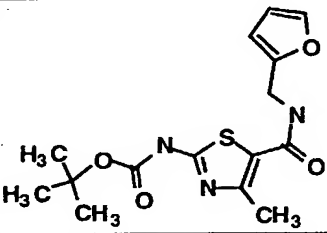
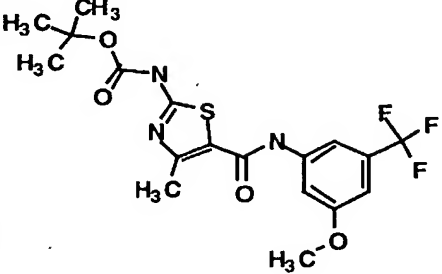
Examples 13 to 53

General Procedure

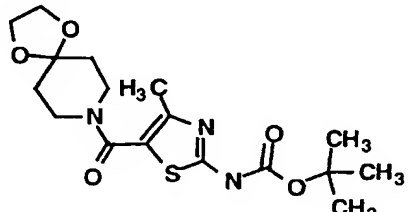
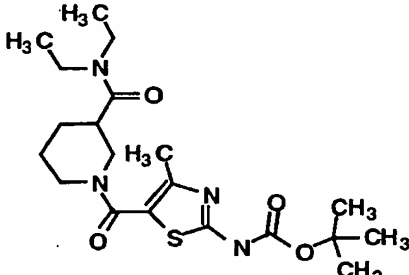
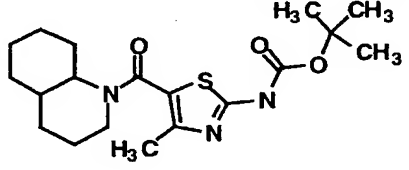
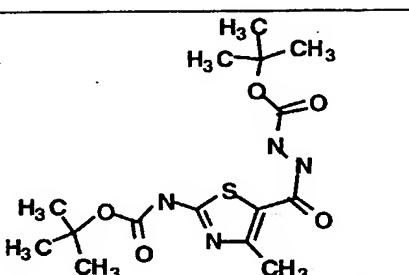
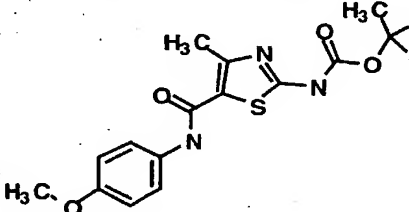
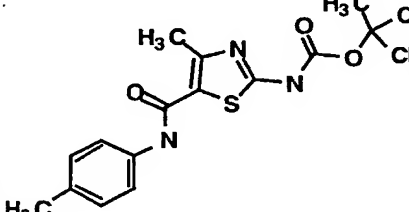
15 Compounds **13** to **53** were prepared following the procedure described below. Appropriate amines (0.40 mmol) and diisopropylethylamine (70 μ L, 0.40 mmol) were added to a suspension of **1C** (100 mg, 0.36 mmol) in dichloromethane (3 mL). The solution was stirred mechanically in a sealed tube at rt for 16 h. The reaction mixtures were diluted with methanol (200 μ L) and loaded in Varian SCX ion exchange columns (2 g/6 cc) pretreated with methanol-dichloromethane (8 mL, 1:1) followed by dichloromethane (8 mL). SCX Column filtration were performed using a Gilson robot unit. The column was washed sequentially with dichloromethane (9 mL), dichloromethane-methanol (9 mL, 4:1), dichloromethane-methanol (9 mL, 1:1), methanol (9 mL), 0.01 M ammonium hydroxide in methanol (9 mL) and 0.05 M ammonium hydroxide in methanol (9 mL). The elutes were collected separately by the robot and then concentrated using a speed vac. Fractions containing the products were combined.

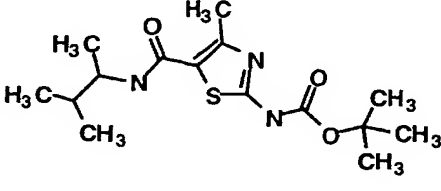
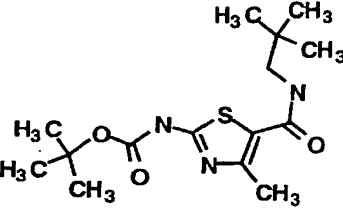
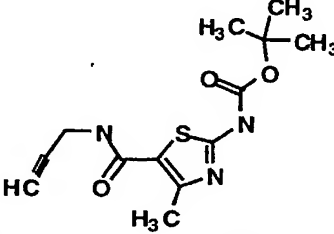
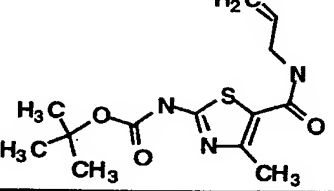
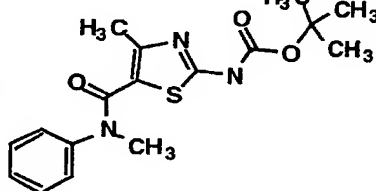
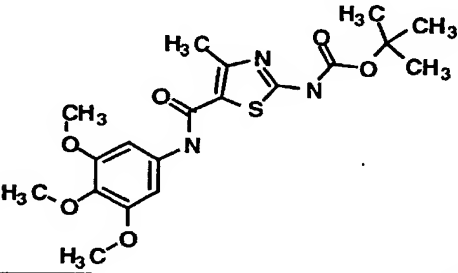
“HPLC Ret Time” is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 50 mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H₂O, 0.2% H₃PO₄) to 100% solvent B (90% MeOH, 10% H₂O, 0.2% H₃PO₄), flow rate 4 mL/min, λ = 220 nM.

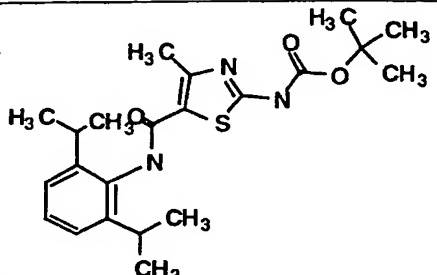
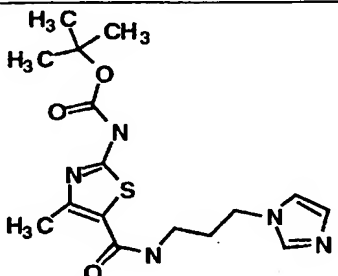
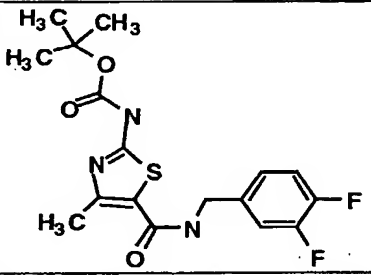
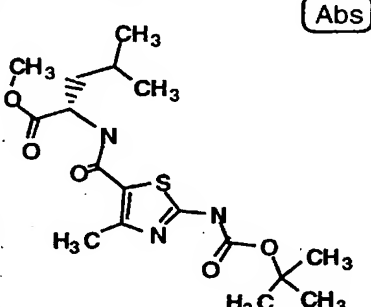
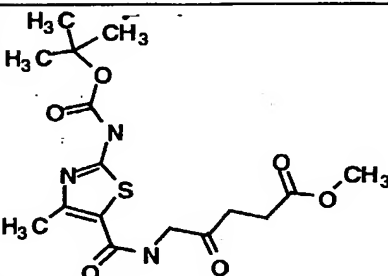
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
13		[5-[[[2-Methoxy-6-methylphenyl]amino]-carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.79
14		[4-Methyl-5-[[[3-methyl-4-(1-methylethyl)phenyl]amino]-carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.51
15		[5-[[[4-Bromo-2,6-dimethylphenyl]amino]-carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.24
16		[4-Methyl-5-[[[2-methyl-6-(1-methylethyl)phenyl]amino]carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.17

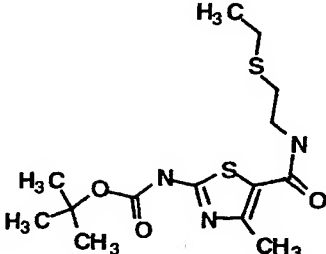
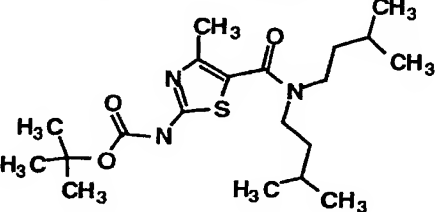
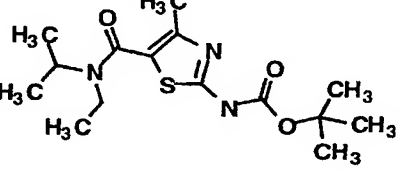
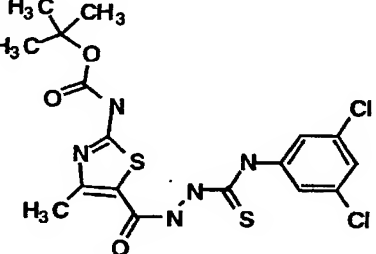
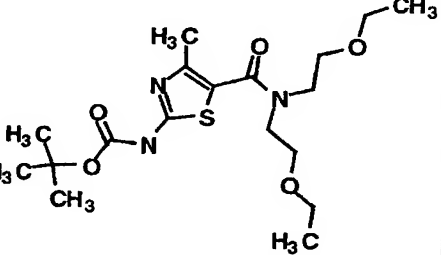
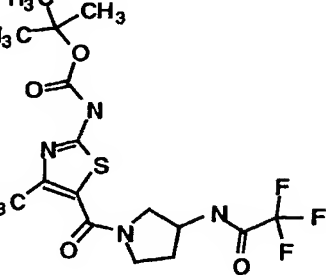
17		[5-[[[2,4-Dimethylphenyl]amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.05
18		[4-Methyl-5-[[[2-methylphenyl]amino]carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.87
19		[5-[[[2-Chloro-6-methylphenyl]amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.86
20		[5-[[[2-(1,1-Dimethylethyl)-4-methylphenyl]amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.30
21		[5-[[[2-Furanylmethyl]amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.54
22		[5-[[[3-Methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.43

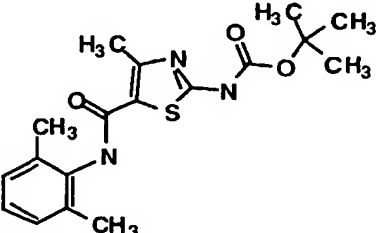
23		[5-[[[(4-Cyclohexylphenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.78
24		[5-[[[(Cyclohexylmethyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.21
25		[5-[[[(2,3-Dihydro-1H-indenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.30
26		[5-[(2,5-Dihydro-1H-pyrrol-1-yl)carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.56
27		[5-[(2,5-Dihydro-2,5-dimethyl-1H-pyrrol-1-yl)carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.86
28		1-[[[2-[[[(1,1-Dimethylethoxy)carbonyl]amino]-4-methyl-5-thiazolyl]carbonyl]-L-prolinamide	2.96
29		[5-[(4-Formyl-1-piperazinyl)carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	2.90

30		[5-(1,4-Dioxa-8-azaspiro[4.5]decan-8-ylcarbonyl)-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.54
31		[5-[[3-[(Diethylamino)carbonyl]-1-piperidinyl]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.66
32		[4-Methyl-5-[(octahydro-1-quinolinyl)carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.37
33		2-[[[(1,1-Dimethylethoxy)carbonyl]amino]-4-methyl-5-thiazolecarboxylic acid 2-[(1,1-dimethylethoxy)carbonyl]hydrazide	3.50
34		[5-[[[(4-Methoxyphenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.83
35		[4-Methyl-5-[[[(4-methylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.07

36		[5-[[[(1,2-Dimethylpropyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.87
37		[5-[[[(2,2-Dimethylpropyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.97
38		[4-Methyl-5-[(2-propynylamino)carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.22
39		[4-Methyl-5-[(2-propenylamino)carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.41
40		[4-Methyl-5-[(methylphenylamino)carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.75
41		[4-Methyl-5-[(3,4,5-trimethoxyphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.84

42		[5-[[[2,6-Bis(1-methylethyl)phenyl]amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.40
43		[5-[[[3-(1H-Imidazol-1-yl)propyl]amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	2.45
44		[5-[[[(3,4-Difluorophenyl)methyl]amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.97
45		N-[[2-[[[(1,1-Dimethylethoxy)carbonyl]amino]-4-methyl-5-thiazolyl]carbonyl]-L-leucine methyl ester	3.99
46		5-[[[2-[[[(1,1-Dimethylethoxy)carbonyl]amino]-4-methyl-5-thiazolyl]carbonyl]amino]-4-oxopentanoic acid methyl ester	3.27

47		[5-[[[2-(Ethylthio)ethyl]amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.75
48		[5-[[Bis(3-methylbutyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.67
49		[5-[[Ethyl(1-methylethyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.84
50		2-[[[(1,1-Dimethylethoxy)carbonyl]amino]-4-methyl-5-thiazolecarboxylic acid 2-[[[3,5-dichlorophenyl]amino]thioxomethyl]hydrazide	4.66
51		[5-[[Bis(2-ethoxyethyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.83
52		[4-Methyl-5-[[[3-[(trifluoroacetyl)amino]-1-pyrrolidinyl]carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.47

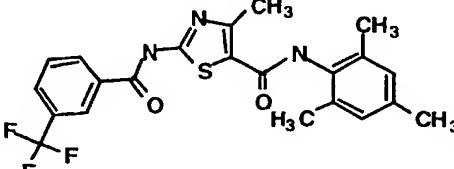
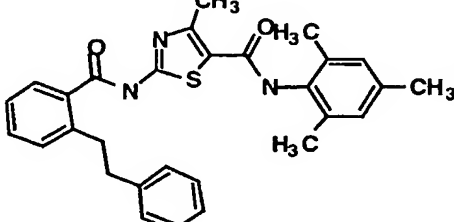
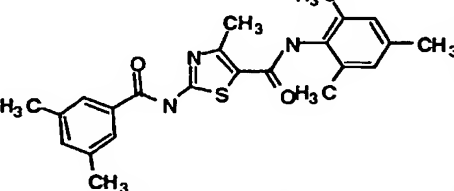
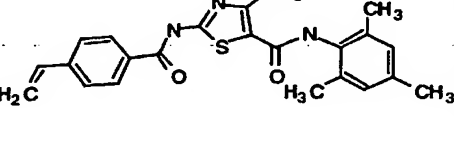
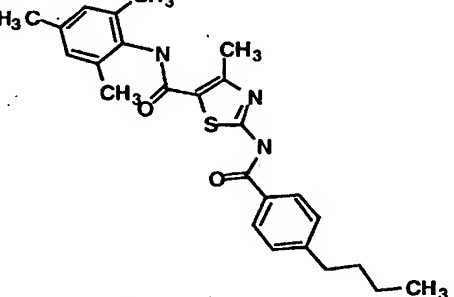
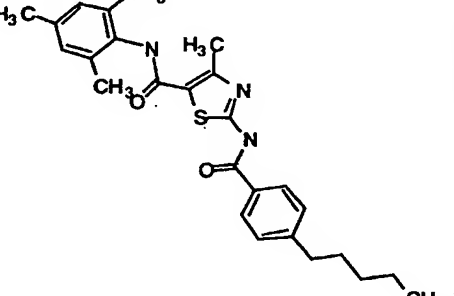
53		[5-[[[(2,6-Dimethylphenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.87
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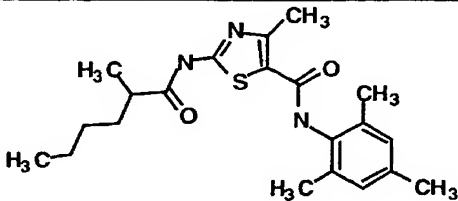
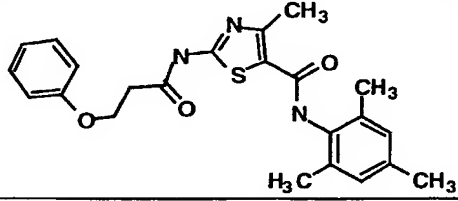
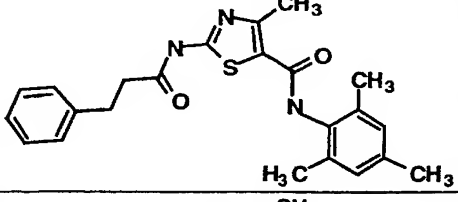
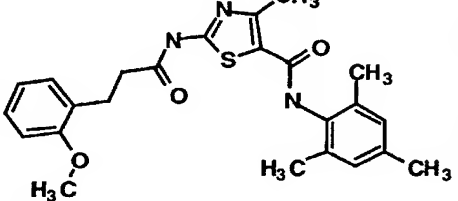
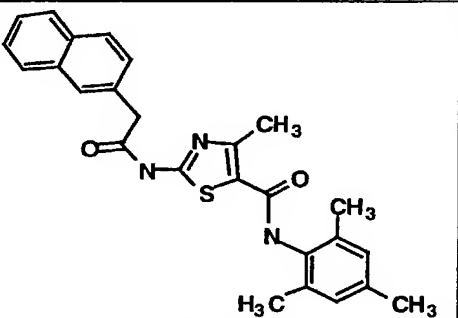
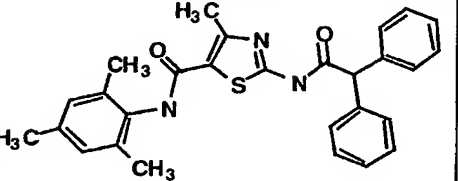
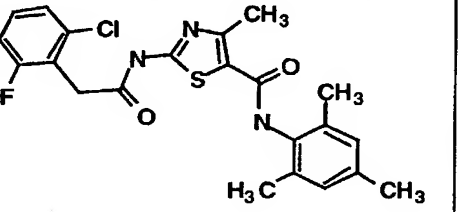
Examples 54 to 129

General Procedure

Compounds **54** to **129** were prepared following the procedure described below. Diisopropylethyl amine (60 μ L, 0.34 mmol) was added to a mixture of amine **2** (30 mg, 0.11 mmol), appropriate carboxylic acid (0.13 mmol), 1-hydroxy-7-azabenzotriazole (19.5 mg, 0.14 mmol), and ethyl-3-(3-dimethylamino)-propyl carbodiimide hydrochloride (26.8 mg, 0.14 mmol) in THF (0.4 mL). The mixture was heated in a sealed tube under argon at 45°C for 24 h. The reaction mixture was diluted with dichloromethane (4 mL) and washed with 2 N aq. HCl solution (2 mL, 3x). The dichloromethane solution was passed through a Varian SCX cation exchange column (2 g, 6 cc) on a Gilson robot. The column was eluted sequentially with acetonitrile-methanol (10 mL, 4:1), methanol-2M methanolic ammonia (3 mL, 4:1), and 2 M methanolic ammonia solution (3 mL, 4x). The fractions were collected separately using the Gilson robot. Fraction containing the product was concentrated and dried *in vacuo*. "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 50 mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H₂O, 0.2% H₃PO₄) to 100% solvent B (90% MeOH, 10% H₂O, 0.2% H₃PO₄), flow rate 4 mL/min, λ = 220 nM for compounds **54** - **127**. For compounds **128** - **129** HPLC conditions are: Zorbax S8-C18 4.5 mm x 7.5 cm short column, 8 min gradient starting from 100% solvent A (10% MeOH, 90% H₂O, 0.2% H₃PO₄) to 100% solvent B (90% MeOH, 10% H₂O, 0.2% H₃PO₄), flow rate 2.5 mL/min, λ = 217 nM.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
54		2-[[2,2-Dichloro-1-methylcyclopropyl]carbonylamino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.22
55		2-[(Cyclohexylacetyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.47
56		2-[(2,5-Difluorobenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.15
57		2-[(5-Bromo-2-chlorobenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.37
58		2-[(3-Cyanobenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.06
59		2-[[4-(Acetylamino)benzoyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.60

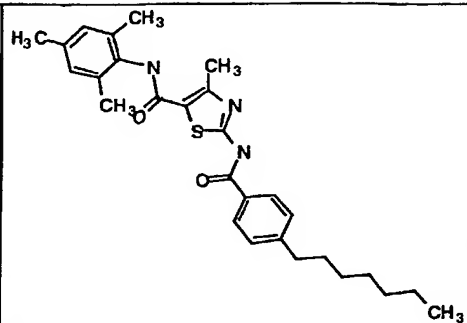
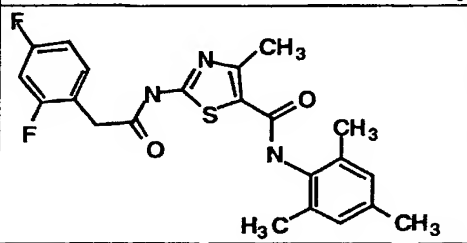
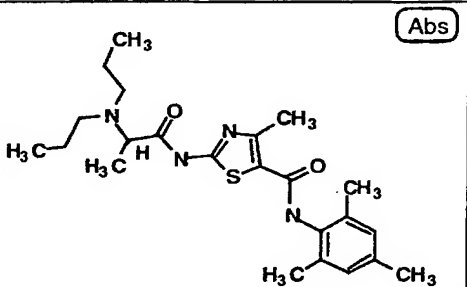
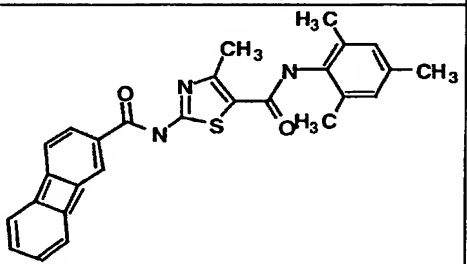
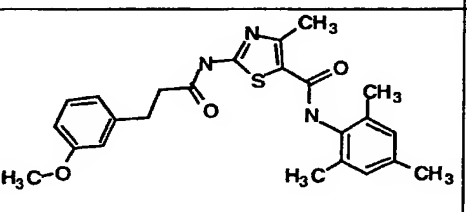
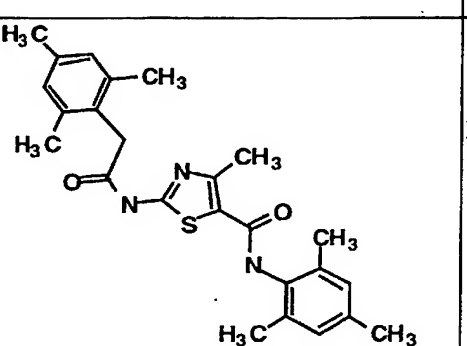
60		4-Methyl-2-[[3-(trifluoromethyl)benzoyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.45
61		4-Methyl-2-[[2-(2-phenylethyl)benzoyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.64
62		2-[(3,5-Dimethylbenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.49
63		2-[(4-Ethenylbenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	
64		2-[(4-Butylbenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.58
65		4-Methyl-2-[(4-pentylbenzoyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.76

66		4-Methyl-2-[(2-methyl-1-oxohexyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.41
67		4-Methyl-2-[(1-oxo-3-phenoxypropyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.21
68		4-Methyl-2-[(1-oxo-3-phenylpropyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.26
69		2-[[3-(2-Methoxyphenyl)-1-oxopropyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.31
70		4-Methyl-2-[(2-naphthalenylacetyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.43
71		2-[(Diphenylacetyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.13
72		2-[[[2-Chloro-6-fluorophenyl]acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.17

73		4-Methyl-2-[[[(2-methylphenyl)acetyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.95
74		2-[[[(3-Methoxyphenyl)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.11
75		2-[[[(3,4-Dimethoxyphenyl)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.90
76		2-[[[(4-Chlorophenyl)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.34
77		2-[[[(1,1'-Biphenyl)-4-ylacetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.60
78		4-Methyl-2-[(1-oxo-4-phenylbutyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.40

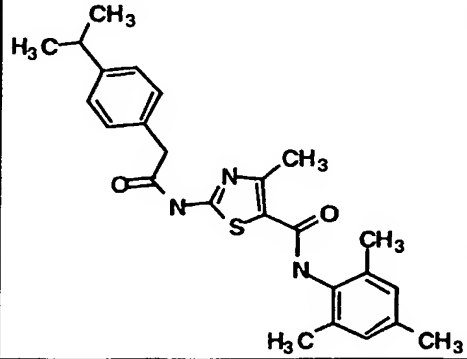
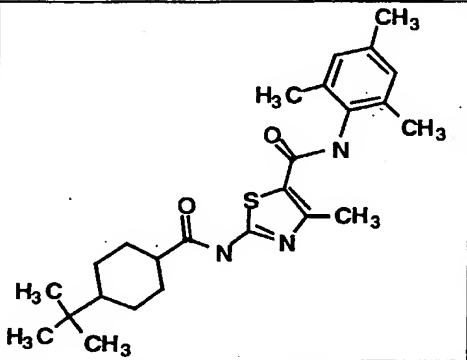
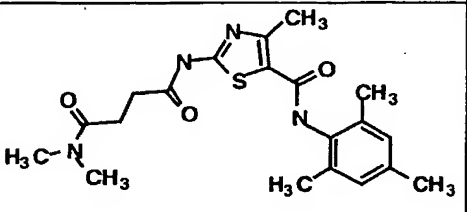
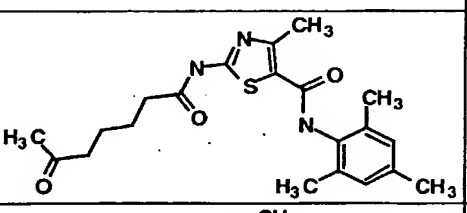
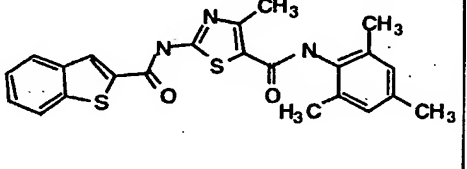
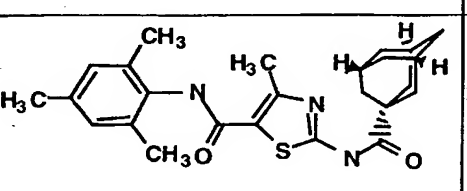
79		4-Methyl-2-[(1-oxooctyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.65
80		2-[(2-Hydroxy-2-phenyl-1-oxopropyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.13
81		2-[(2-Hydroxy-1-oxohexyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.14
82		4-Methyl-2-[[1-oxo-4-(2-thienyl)butyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.32
83		4-Methyl-2-[(3-thienylcarbonyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.04
84		2-[(2-Benzofuranylcarbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.37
85		N-[4-Methyl-5-[[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]-4-pyridinecarboxamide, N-oxide	3.50
86		6-Chloro-N-[4-methyl-5-[[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]-3-pyridinecarboxamide	4.08

87		N-[4-Methyl-5-[[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]-3-pyridinecarboxamide	3.56
88		N-[4-Methyl-5-[[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]-3-quinolinecarboxamide	4.11
89		4-Methyl-2-[[[(4-nitrophenyl)acetyl]-amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.08
90		4-Methyl-2-[(2,4,6-trichlorobenzoyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.45
91		4-Methyl-2-[[2-[[[3-(trifluoromethyl)phenyl]amino]benzoyl]-amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.86
92		4-Methyl-2-[[4-(4-nitrophenyl)-1-oxobutyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.28
93		4-Methyl-2-[[4-(4-methylsulfonyl)benzoyl]-amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.79

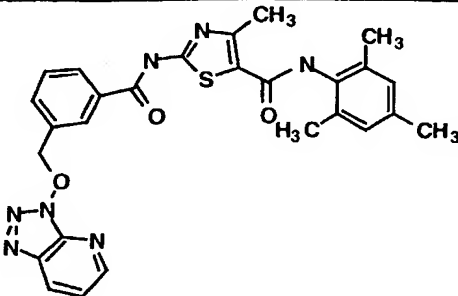
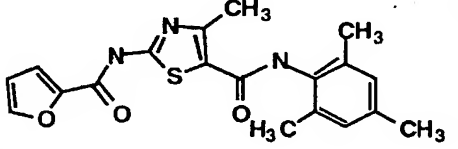
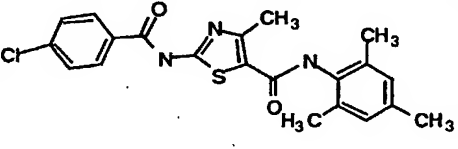
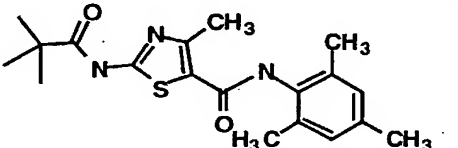
94		2-[(4-Heptylbenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	
95		2-[[[(2,4-Difluorophenyl)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.15
96	 (Abs)	(S)-2-[[[2-(Dipropylamino)-1-oxopropyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.20
97		2-[(2-Biphenyl-enecarbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.64
98		2-[[[3-(3-Methoxyphenyl)-1-oxopropyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.26
99		4-Methyl-N-(2,4,6-trimethylphenyl)-2-[[[(2,4,6-trimethylphenyl)acetyl]amino]-5-thiazolecarboxamide	4.52

100		4-Methyl-2-[(1-oxo-6-heptenyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.47
101		2-[[[(1,3-Benzodioxol-5-yl)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.07
102		4-Methyl-2-[[[2-(phenylmethoxy)phenyl]acetyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.46
103		4-Methyl-2-[[[3-phenoxyphenyl]acetyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.56
104		2-[(3,5-Dimethoxyphenyl)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.13
105		2-[[4-[4-[Bis(2-chloroethyl)amino]phenyl]-1-oxobutyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.75
106		4-[[[4-[[[4-methyl-5-[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]-amino]-carbonyl]phenyl]-amino]-4-oxobutanoic acid methyl ester	4.03

107		4-Methyl-2-[[(phenylsulfonyl)acetyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.77
108		2-[[2-(Acetyl)amino]-1-oxohexyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.99
109		2-[[4-[(Dipropylamino)sulfonyl]benzoyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.51
110		2-[(4-Cyclohexylbenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.94
111		2-[(4-Bromo-3-methylbenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.80
112		2-[[(2,3-Difluorophenyl)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.14

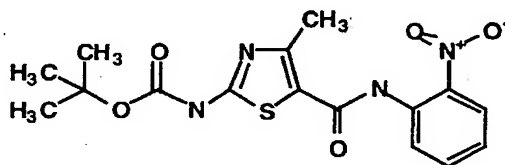
113		4-Methyl-2-[[[4-(1-methylethyl)phenyl]acetyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.56
114		2-[[[4-(1,1-Dimethyl-ethyl)cyclohexyl]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.85
115		N,N-Dimethyl-N'-[4-methyl-5-[[2,4,6-trimethylphenyl]amino]carbonyl]-2-thiazolyl]butanediamide	3.50
116		2-[(1,6-Dioxohexyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.40
117		2-[(Benzo[b]thiophen-2-ylcarbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.53
118		2-[(1-Adamantyl-carbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.66

119		4-Methyl-2-[[[(4-methylcyclohexyl) carbonyl] amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.48
120		2-[(1,7-Dioxooctyl)-amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.88
121		2-[[2-(Acetylthio)-4-(ethylthio)-1-oxobutyl] amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.93
122		1,5-Dimethyl-N-[4-methyl-5-[[[(2,4,6-trimethylphenyl) amino] carbonyl]-2-thiazolyl]-1H-pyrazole-3-carboxamide	3.91
123		2-[[[4-methyl-5-[[[(2,4,6-trimethylphenyl) amino] carbonyl]-2-thiazolyl] amino] carbonyl] benzoic acid	3.70
124		N-[4-Methyl-5-[[[(2,4,6-trimethylphenyl) amino] carbonyl]-2-thiazolyl]-6-benzothiazolecarboxamide	4.18
125		1-Ethyl-4-methyl-N-[4-methyl-5-[[[(2,4,6-trimethylphenyl) amino] carbonyl]-2-thiazolyl]-1H-pyrazole-3-carboxamide	4.09

126		4-Methyl-2-[[3-[(3H-1,2,3-triazolo[4,5-b]pyridin-3-yloxy)methyl]benzoyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.15
127		2-[(2-furanylcarbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.45
128		2-[(4-chlorobenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.85
129		2-[(2,2-dimethyl-1-oxopropyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.30

Example 130

Preparation of [4-Methyl-5[[[(2-nitrophenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester



5

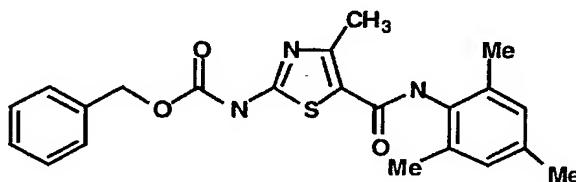
2-Nitroaniline (55 mg, 0.4 mmol) and diisopropylethylamine (70 μ L, 0.4 mmol) were added dropwise to a stirred solution of 2-*tert*-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylic acid chloride 1C (100 mg, 0.36 mmol) in dichloromethane (3 mL). After 16 h at rt, 4-*N,N*-dimethylaminopyridine (22 mg, 0.18 mmol) was added and the mixture

was stirred for additional 3.5 h. The solvent was evaporated *in vacuo*. The residue was chromatographed on a silica gel column. Elution with 5% EtOAc in hexanes followed by 20% EtOAc in hexanes afforded the title compound (15 mg, 11%) as a yellow solid.

5

Example 131

Preparation of [4-Methyl-5[[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, phenylmethyl ester



10

A. Ethyl-2-benzyloxycarbonyloxyamino-4-methyl-thiazole-5-carboxylate

A 3 M aq. NaHCO₃ solution (10 mL, 30 mmol) was added to a stirred solution of ethyl-2-amino-4-methyl-thiazole-5-carboxylate (372 mg, 2 mmol) in THF (20 mL) at 0-5°C. Benzyl chloroformate (500 µL) was added.

15 After 2 h, additional benzyl chloroformate (500 µL) and the biphasic solution was stirred for an additional 2 h at 0-5°C. The mixture was diluted with dichloromethane (50 mL) and water (30 mL). The organic layer was separated, dried (MgSO₄), filtered and concentrated. The residue was chromatographed on a silica gel column. Elution with 10% EtOAc in
20 hexanes followed by 20% and 30% EtOAc in hexanes afforded the title compound (310 mg, 48%) as a white solid.

B. 2-Benzyloxycarbonyloxyamino-4-methyl-thiazole-5-carboxylic acid

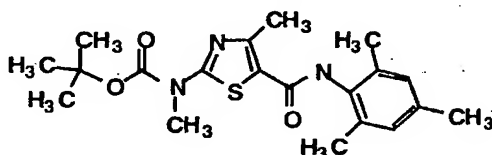
Compound **131B** was prepared by an analogous method as that of **3B**,
25 except using **131A** to give the title compound **131B** as a white powder (77%).

C. [4-Methyl-5-[(2,4,6-Trimethylphenyl)aminocarbonyl]-2-thiazolyl]carbamic acid, phenylmethyl ester

Diisopropylethylamine (70 μ L, 0.41 mmol) was added to a solution of **131B** (100 mg, 0.34 mmol), 2,4,6-trimethylaniline (60 μ L, 0.41 mmol), and [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium]hexafluorophosphate (HATU, 160 mg, 0.41 mmol). The mixture was stirred at rt for 24 h, diluted with EtOAc (20 mL) and washed with 2 N Aq. HCl solution (3x), brine, dried (Na_2SO_4), filtered and concentrated. The residue was triturated with ether (40 mL) to obtain the title compound (100 mg, 77%) as an off-white solid.

Example 132

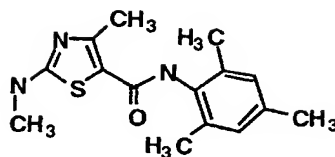
Preparation of Methyl[4-methyl-5-[(2,4,6-trimethylphenyl)aminocarbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester



Compound **132** was prepared by an analogous method as that of **1**, except using ethyl-2-*tert*-butoxycarbonyloxyaminomethyl-4-methyl-thiazole-5-carboxylate to give the title compound **132** as a tan solid.

Example 133

Preparation of 4-Methyl-2-(methylamino)-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide, trifluoroacetate (1:1)

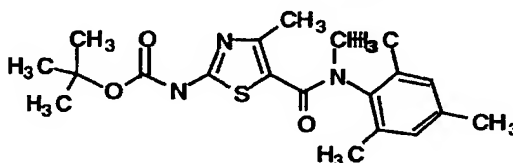


Compound **133** was prepared by an analogous method as that of **4**, except using **132** to give the title compound **133** as a white solid (91%).

5

Example 134

Preparation of [4-Methyl-5-[[methyl(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester



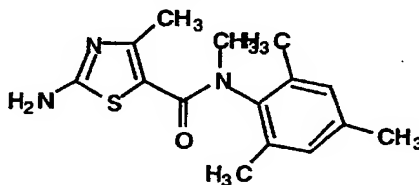
10

Compound **134** was prepared by an analogous method as that of **1**, except using N-methyl-2,4,6-trimethylaniline to give the title compound **134** as a white solid (60%).

15

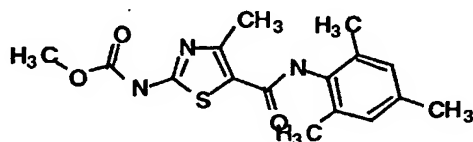
Example 135

Preparation of 2-Amino-N,4-dimethyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide, trifluoroacetate (1:1)



20

Compound **135** was prepared by an analogous method as that of **4**, except using **134** to give the title compound **135** as a white solid (97%).

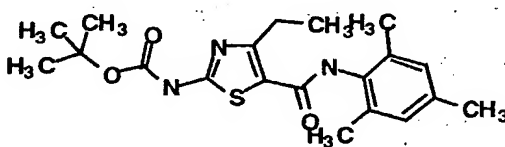
Example 136Preparation of [4-Methyl-5[[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, methyl ester

5

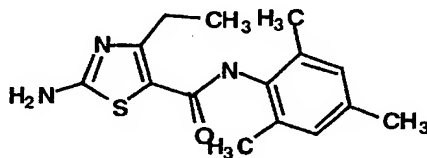
A mixture of **2** (100 mg, 0.36 mmol), pyridine (87 μ L, 1.08 mmol), methyl chloroformate (111 μ L, 1.44 mmol) in dichloromethane (3 mL) was stirred at rt for 1.5 h. The solution was diluted with dichloromethane and washed with aq. NaHCO_3 solution (20 mL, 2x), brine; dried (MgSO_4), filtered and concentrated. The residue was triturated with ether to obtain the title compound (88 mg, 82%) as a white solid.

Example 137

15 Preparation of [4-Ethyl-5[[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester



Compound **137** was prepared by an analogous method as that of **1**, except using methyl-2-amino-4-ethyl-thiazole-5-carboxylate to give the title compound **137** as a white solid (70%).

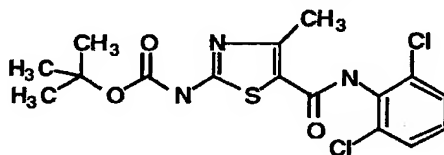
Example 138Preparation of 2-Amino-4-ethyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide, trifluoroacetate

5

Compound **138** was prepared by an analogous method as that of **4**, except using **137** to give the title compound **138** as a white solid (89%).

Example 139

10 Preparation of [5-[(2,6-Dichlorophenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

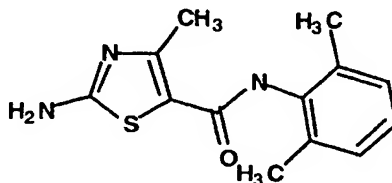


15 A 1 M solution of sodium bis-trimethylsilyl amide (290 μ L, 0.29 mmol) was added to a stirred solution of 2,6-dichloroaniline (13.4 mg, 0.08 mmol) in THF (1 mL). After 30 min, the mixture was cooled to 0 $^{\circ}$ C and **1C** (30 mg, 0.11 mmol) was added in one portion. The mixture was allowed to warm to rt and stirred for 16 h. The solution was diluted with dichloromethane and washed with 2 N aq. HCl solution (2 mL, 3x), dried (MgSO₄), filtered and

20 concentrated. The residue was chromatographed on a silica gel column and eluted with 30% EtOAc in hexanes to obtain the title compound (20 mg, 45%) as a light yellow solid.

Example 140

Preparation of 2-Amino-N-(2,6-dimethylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)

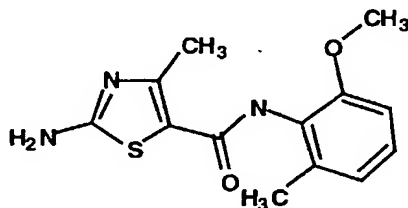


- 5 Compound 140 was prepared by an analogous method as that of 4, except using 53 to give the title compound 140 as a light tan solid (100%).

Example 141

Preparation of 2-Amino-N-(2-methoxy-6-methylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)

10

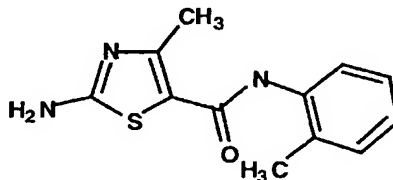


Compound 141 was prepared by an analogous method as that of 4, except using 13 to give the title compound 141 as an off-white solid (100%).

15

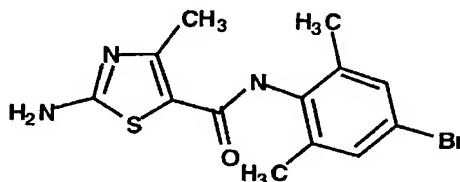
Example 142

Preparation of 2-Amino-N-(2-methylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



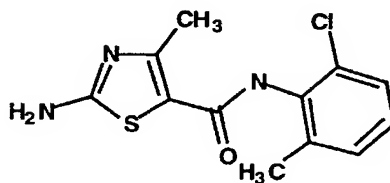
20

Compound 142 was prepared by an analogous method as that of 4, except using 18 to give the title compound 142 as a light tan solid (90%).

Example 143Preparation of 2-Amino-N-(2,6-dimethyl-4-bromophenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)

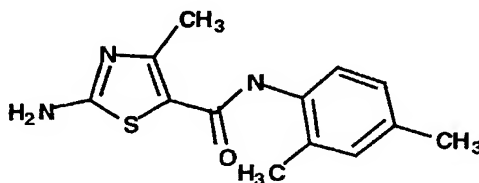
5

Compound **143** was prepared by an analogous method as that of **4**, except using **15** to give the title compound **143** as a light tan solid (70%).

Example 144Preparation of 2-Amino-N-(2-chloro-6-methylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)

10

15 Compound **144** was prepared by an analogous method as that of **4**, except using **19** to give the title compound **144** as a light tan solid (81%).

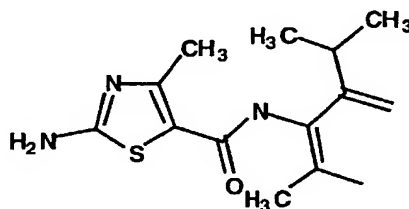
Example 145Preparation of 2-Amino-N-(2,4-dimethylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)

20

Compound 145 was prepared by an analogous method as that of 4, except using 17 to give the title compound 145 as a light tan solid (68%).

Example 146

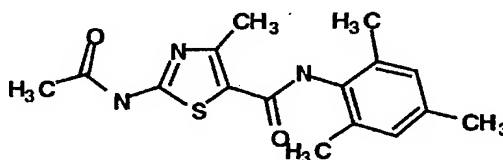
5 Preparation of 2-Amino-N-(2-methyl-6-isopropylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



Compound 146 was prepared by an analogous method as that of 4, except
10 using 16 to give the title compound 146 as a light tan solid (100%).

Example 147

15 Preparation of 2-(Acetylamino)-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



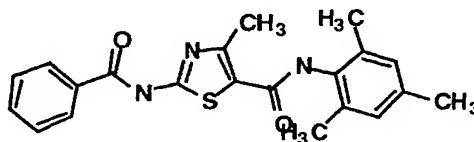
15

A mixture of 2 (54 mg, 0.2 mmol), acetic anhydride (22 μ L, 0.23 mmol), dimethylaminopyridine (3 mg) in dichloromethane (4.5 mL) was stirred at rt for 4.5 h. The mixture was diluted with dichloromethane (65 mL) and
20 washed with 1 N aq. HCl solution (20 mL), water; dried (MgSO_4), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 35% EtOAc in hexanes to obtain the title compound (43 mg, 69%) as a white solid.

25

Example 148

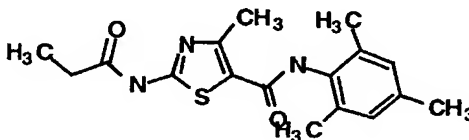
Preparation of 2-(Benzoylamino)-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



- 5 A solution of **2** (100 mg, 0.36 mmol) and benzoic anhydride (226 mg, 1 mmol) in dichloromethane (10 mL) and pyridine (2 mL) was stirred at rt overnight. The mixture was diluted with dichloromethane (50 mL) and washed with 2 N aq. HCl solution (15 mL, 2x), 10% aq. NaHCO₃ solution (20 mL, 2x); dried (MgSO₄), filtered and concentrated. The residue was
- 10 chromatographed on a silica gel column and eluted with 30% EtOAc in hexanes followed by 50% EtOAc in hexanes to obtain the title compound contaminated with benzoic acid. The solid was dissolved in EtOAc (40 mL) and washed with satd. KHCO₃ solution (15 mL, 4x), dried (MgSO₄), filtered and concentrated to obtain the title compound (110 mg, 80%) as a
- 15 white solid.

Example 149

Preparation of 4-methyl-2-[(1-oxopropyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



20

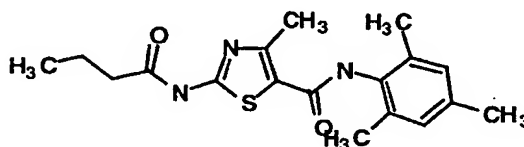
- A mixture of **2** (100 mg, 0.36 mmol), propionic anhydride (332 μ L, 2.58 mmol) in dichloromethane (10 mL) and pyridine (4 mL) was stirred at rt for 3 h. Dimethylaminopyridine (122 mg, 1 mmol) was added and the
- 25 mixture was stirred for additional 1.5 h. The mixture was diluted with dichloromethane and washed with 1 N aq. HCl solution (25 mL, 3x), aq.

NaHCO₃ solution (20 mL, 2x), water (20 mL), brine; dried (MgSO₄), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 20% EtOAc in hexanes to obtain the title compound (81 mg, 68%) as a white solid.

5

Example 150

Preparation of 4-methyl-2-[(1-oxobutyl)aminol]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



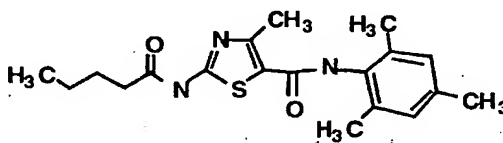
10

Compound **150** was prepared by an analogous method as that of **149**, except using butyric anhydride to give the title compound **150** as a white solid (76%).

15

Example 151

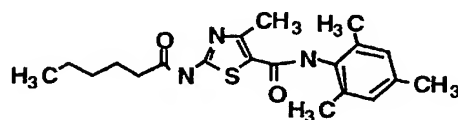
Preparation of 4-methyl-2-[(1-oxopentyl)aminol]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



20 Compound **151** was prepared by an analogous method as that of **149**, except using valeric anhydride to give the title compound **151** as a white solid (77%).

Example 152

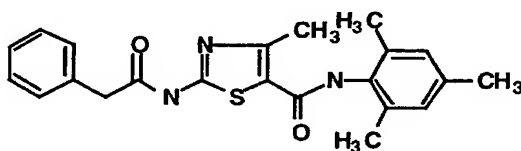
Preparation of 4-methyl-2-[(1-oxohexyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



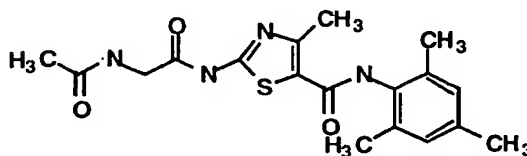
- 5 Compound **152** was prepared by an analogous method as that of **149**, except using hexanoic anhydride to give the title compound **152** as a white solid (75%).

Example 153

- 10 Preparation of 4-Methyl-2-[(phenylcetyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



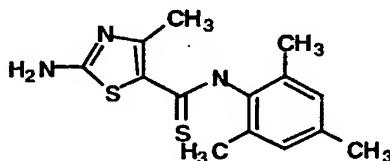
- A solution of amine **2** (50 mg, 0.18 mmol), diisopropylethylamine (101 μ L, 0.58 mmol), phenylacetic acid (27.2 mg, 0.20 mmol), 1-hydroxy-7-azabenzotriazole (29.4 mg, 0.22 mmol), and ethyl-3-(3-dimethylamino)-propyl carbodiimide hydrochloride (42.2 mg, 0.22 mmol) in dichloromethane (0.62 mL) was mechanically stirred in a sealed vial for 16 h. The reaction mixture was passed through a Varian SCX ion exchange column (2 g/6 cc) and eluted with acetonitrile-methanol (10 mL, 4:1) followed by 2 M methanolic ammonia solution (9 mL). Fractions containing the product were combined and then concentrated. The residue was dissolved in dichloromethane and washed with 2 N aq. HCl solution (3x), dried (Na_2SO_4), filtered and concentrated to obtain the title compound (39 mg, 55%) as a tan solid.

Example 154Preparation of 2-[[[(Acetylamino)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-6-thiazolecarboxamide

5

A solution of amine **2** (50 mg, 0.18 mmol), diisopropylethylamine (400 μ L, 2.3 mmol), N-acetylglycine (42 mg, 0.36 mmol), 1-hydroxy-7-azabenzotriazole (49 mg, 0.36 mmol), and ethyl-3-(3-dimethylamino)-propyl carbodiimide hydrochloride (72 mg, 0.36 mmol) in THF (5 mL) was heated to 50°C overnight. The mixture was cooled, diluted with dichloromethane (60 mL) and washed with 2 N aq. HCl solution (20 mL), satd. aq. KHCO_3 solution (20 mL), dried (MgSO_4), filtered and concentrated. The crude solid was triturated with ether (10 mL), filtered, and washed with ether (5 mL, 3x) to obtain the title compound (40 mg, 59%) as an off-white solid.

15

Example 155Preparation of 2-Amino-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarbothioamide

20

A suspension of **2** (50 mg, 0.18 mmol) and Lawesson reagent (44 mg, 0.11 mmol) in toluene (0.23 mL) was heated to 100°C for 4h. Additional Lawesson reagent (44 mg, 0.11 mmol) was added and the mixture was heated for additional 3.5 h. The crude mixture was chromatographed on a

25

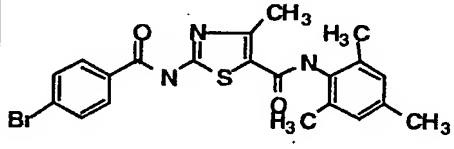
silica gel column and eluted with 50% EtOAc in hexanes followed by 70% EtOAc in hexanes to obtain a a yellow solid which was triturated with hexanes (6 mL) to obtain the title compound (11 mg, 21%) as a yellow solid.

5

Examples 156 to 170

General Procedure

Compounds **156** to **170** were prepared following the procedure described below. Diisopropylethyl amine (60 μ L, 0.34 mmol) was added to a mixture of amine **2** (30 mg, 0.11 mmol), appropriate carboxylic acid (0.13 mmol), 1-hydroxy-7-azabenzotriazole (19.5 mg, 0.14 mmol), and ethyl-3-(3-dimethylamino)-propyl carbodiimide hydrochloride (26.8 mg, 0.14 mmol) in THF (1 mL). The mixture was heated in a sealed tube under argon at 45 °C for 24 h. The reaction mixture was diluted with dichloromethane (4 mL) and washed with 2 N aq. HCl solution (2 mL, 3x), dried (Na_2SO_4) and concentrated using a speedvac. The crude products were either triturated with dichloromethane-ether (5 mL, 1:1) or purified by silica gel chromatography (elution solvent: 50% EtOAc in hexanes and EtOAc). "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 50 mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H_2O , 0.2% H_3PO_4) to 100% solvent B (90% MeOH, 10% H_2O , 0.2% H_3PO_4), flow rate 4 mL/min, λ = 220 nM.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
156		2-[(4-Bromobenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.03

157		4-Methyl-2-[(4-nitrobenzoyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.87
158		2-[(4-cyanobenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.70
159		4-Methyl-2-[[5-nitro-2-furanyl)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.63
160		4-Methyl-2-[(2-thienylcarbonyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.60
161		4-[[[4-Methyl-5-[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]amino]carbonyl]benzoic acid methyl ester	4.99
162		2-[(5-isoxazolylcarbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.87
163		2-[(3-furanylcarbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.54
164		2-[[2,4-dimethyl-5-thiazolyl)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.74

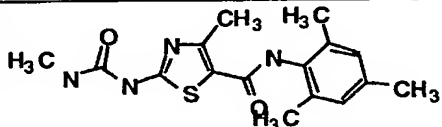
165		2-[[[4-Methoxy-3-thienyl)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.75
166		4-Methyl-2-[[[5-nitro-3-thienyl)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.78
167		2-[[[4-[(4-Chlorophenyl)thio]-3-thienyl)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.27
168		2-[[[5-Chloro-4-methoxy-3-thienyl)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.04
169		2-[[[2-(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)-3-thienyl)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.13
170		2-[[[2-Acetyl-3-thienyl)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.54

Examples 171 to 180

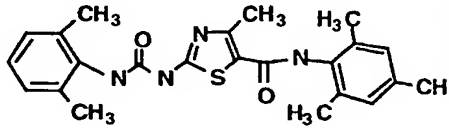
General Procedure

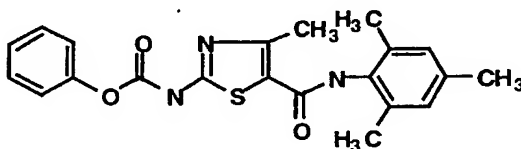
Compounds 171 to 180 were prepared following the procedure described
5 below.

- A mixture of **2** (80 mg, 0.29 mmol), appropriate isocyanate (0.87 mmol) and pyridine (2 mL) in THF (3.5 mL) was stirred at rt overnight. In some cases the reaction mixture was heated to 60-70°C for 5 h. Some of these reactions were carried out at rt overnight in the presence of catalytic N,N-
- 5 dimethylaminopyridine. The reaction mixture was diluted with dichloromethane and washed with 1 N aq. HCl solution (3x), water, brine; dried (MgSO₄), filtered and concentrated. The crude product was purified either by trituration with ether or ether-hexanes mixture, or by
- 10 chromatography on a silica gel column (elution solvent 20-40% EtOAc in hexanes) followed by trituration or by passing through Varian cation exchange SCX cartridge and sequentially eluted with methanol (5 mL), dichloromethane (5 mL), acetonitrile-methanol (10 mL, 4:1) and methanol-2 M methanolic ammonia (10 mL, 4:1) to obtain the title compound.
- "HPLC Ret Time" is the HPLC retention time under the following
- 15 conditions: For compounds **171-172**, **175**, and **177** HPLC conditions are: Zorbax S8-C18 4.5 mm x 7.5 cm short column, 30 min gradient starting from 100% solvent A (10% MeOH, 90% H₂O, 0.2% H₃PO₄) to 100% solvent B (90% MeOH, 10% H₂O, 0.2% H₃PO₄), flow rate 2.5 mL/min, λ = 217 nM.
- For the other compounds HPLC conditions are: Zorbax S8-C18 4.5 mm x
- 20 7.5 cm short column, 8 min gradient starting from 100% solvent A (10% MeOH, 90% H₂O, 0.2% H₃PO₄) to 100% solvent B (90% MeOH, 10% H₂O, 0.2% H₃PO₄), flow rate 2.5 mL/min, λ = 217 nM.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
171		4-Methyl-2-[[[(methylamino)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazole-carboxamide	24.48

172		4-Methyl-2-[[[(phenyl-amino)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazole-carboxamide	30.45
173		4-Methyl-2-[[[(4-methylphenyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazole-carboxamide	8.81
174		4-Methyl-2-[[[(phenylmethyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.52
175		2-[[[(Butylamino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	30.49
176		4-Methyl-2-[[[(propylamino)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	7.41
177		2-[[[(Cyclohexylamino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	27.21
178		2-[[[(2-Chlorophenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.99
179		2-[[[(3-Fluorophenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.87

180		2-[[[[(2,6-Dimethyl-phenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	8.92
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Example 181Preparation of [5-[[[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid, phenyl ester

A 10% aq. KHCO_3 solution (170 mL) was added to a stirred solution of 2 (1.02 g, 3.7 mmol) in THF (130 mL). Phenylchloroformate (1.39 mL, 11.1 mmol) was added dropwise. The biphasic mixture was stirred at rt overnight, diluted with dichloromethane (200 mL) and washed with water (50 mL, 2x) and brine. The organic extract was separated, dried (MgSO_4), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 10% EtOAc in hexanes to obtain the title compound (980 mg, 69%) as a solid.

Examples 182 to 236*General Procedure*

Compounds 182 to 236 were prepared following the procedure described below.

A solution of phenylcarbamate 181 (20 mg, 0.054 mmol) and the appropriate amine (0.08 mmol) in THF-acetonitrile (3 mL, 1:1) was stirred at rt overnight. Some of the reactions required heating to 60 °C for 4 h to overnight. The mixture was diluted with dichloromethane (4 mL) and washed with 1 N aq. HCl solution (1.5 mL, 2x), 1 N aq. NaOH solution

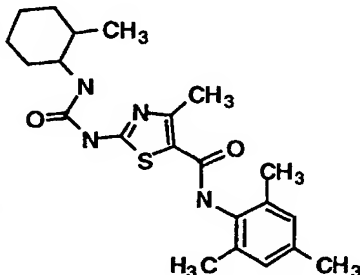
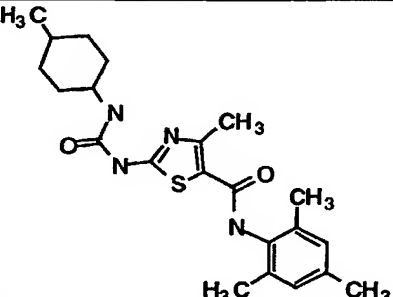
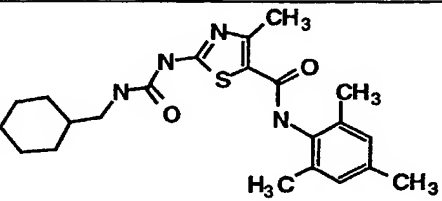
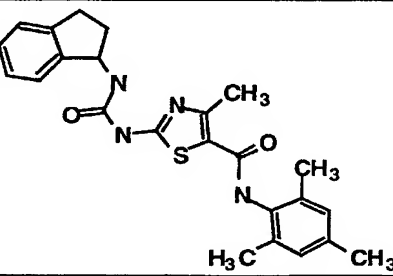
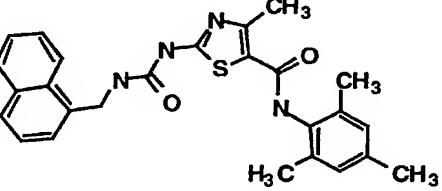
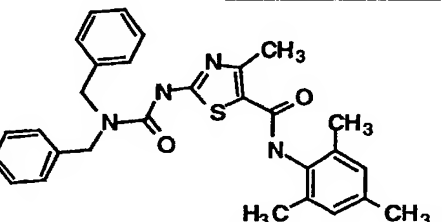
(1.5 mL, 2x). The dichloromethane extract was separated, dried (MgSO₄), filtered and concentrated to obtain the title product.

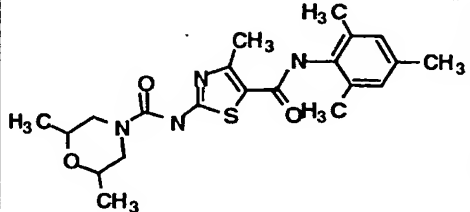
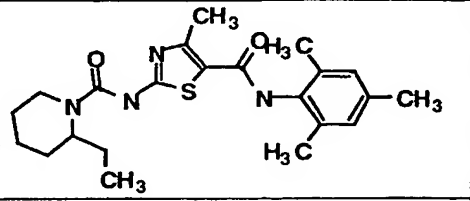
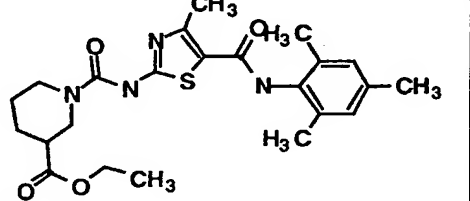
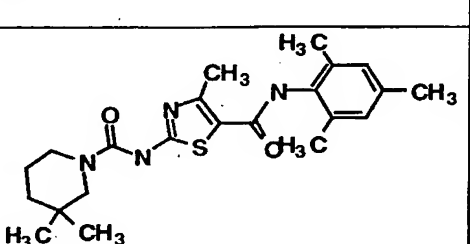
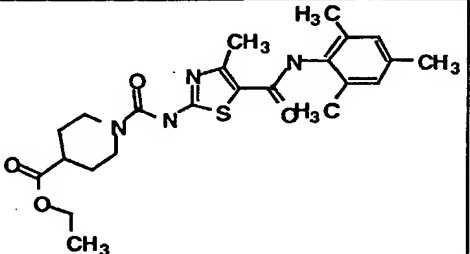
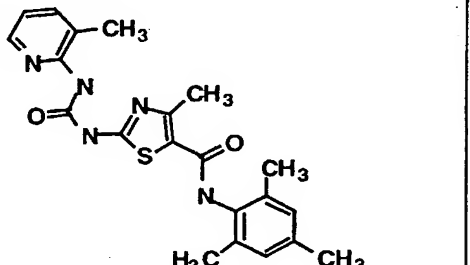
"HPLC Ret Time" is the HPLC retention time under the following conditions: For compounds 182-192 HPLC conditions are: Zorbax SB-C18

- 5 4.5 mm x 7.5 cm short column, 8 min gradient starting from 100% solvent A (10% MeOH, 90% H₂O, 0.2% H₃PO₄) to 100% solvent B (90% MeOH, 10% H₂O, 0.2% H₃PO₄), flow rate 2.5 mL/min, λ = 217 nm. For compounds 193-236 HPLC conditions are: YMC S5 ODS 4.6 x 50 mm Ballistic
- 10 Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H₂O, 0.2% H₃PO₄) to 100% solvent B (90% MeOH, 10% H₂O, 0.2% H₃PO₄), flow rate 4 mL/min, λ = 220 nm.

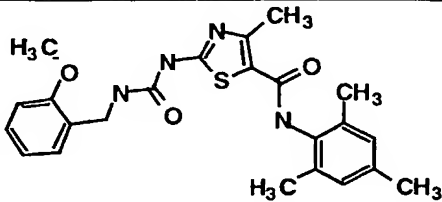
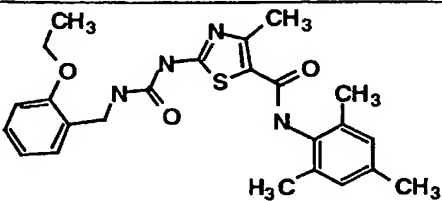
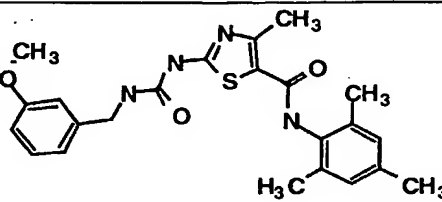
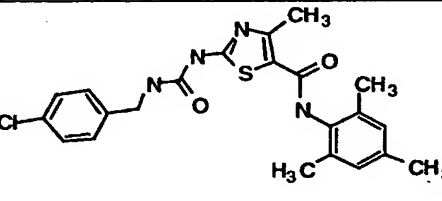
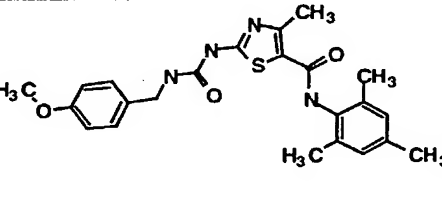
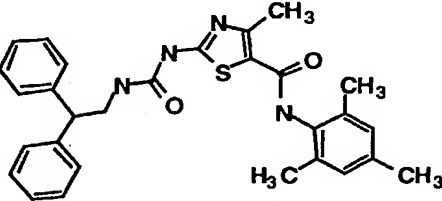
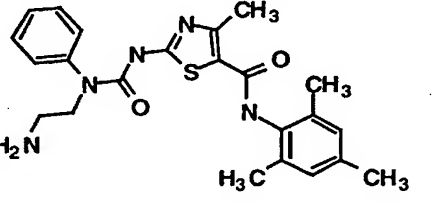
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
182		4-Methyl-2-[[[(2-phenylethyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.83
183		2-[[[(Hexylamino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	9.01
184		2-[[[(1,1-Dimethylethyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.48
185		2-[[[(3-Fluoro-4-methylphenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.92

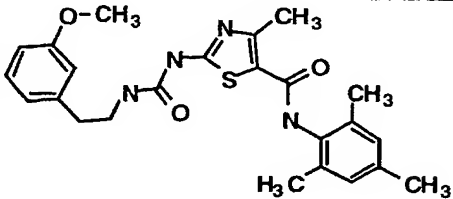
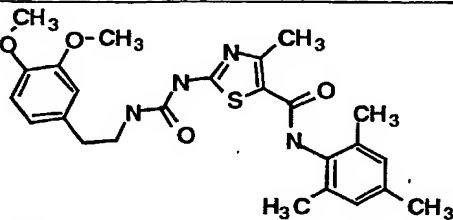
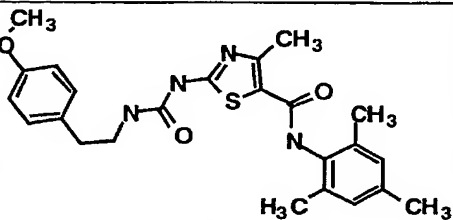
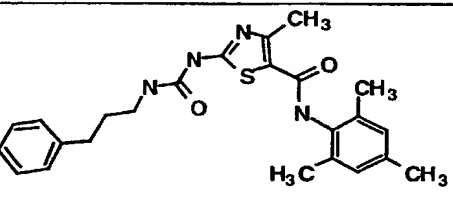
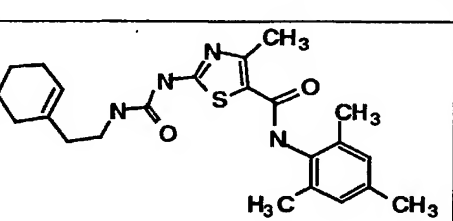
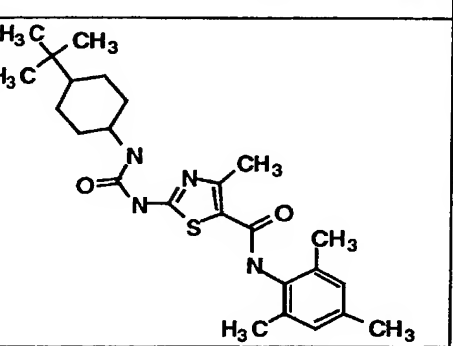
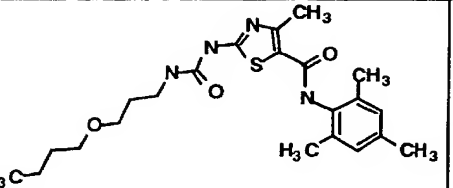
186		2-[[[(4-Methoxyphenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.57
187		2-[[[(Diethylamino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.19
188		2-[[[Bis(1-methylethyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.90
189		4-Methyl-2-[[[methyl(phenylmethyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.56
190		4-Methyl-2-[[[(methylphenylamino)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.39
191		2-[[[(Cyclohexylmethyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.84
192		4-Methyl-2-[[[(1-phenylethyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.47
193		2-[[[(Cyclopropylmethyl)propylamino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.36

194		4-Methyl-2-[[[(2-methylcyclohexyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.42
195		4-Methyl-2-[[[(4-methylcyclohexyl)-amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.49
196		2-[[[(Cyclohexylmethyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.49
197		2-[[[(2,3-Dihydro-1H-inden-1-yl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.35
198		4-Methyl-2-[[[(1-naphthalenylmethyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.43
199		2-[[[Bis(phenylmethyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.66

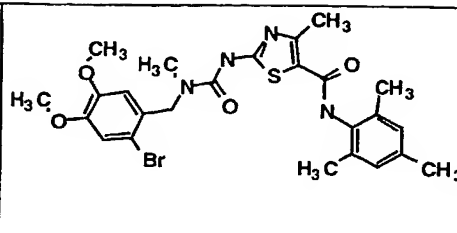
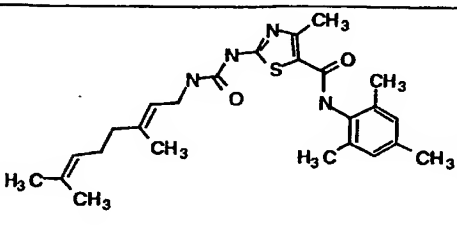
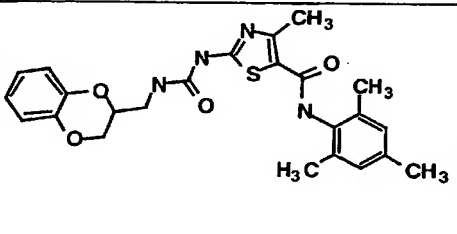
200		2,6-Dimethyl-N-[4-methyl-5-[[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]-4-morpholinecarboxamide	3.97
201		2-Ethyl-N-[4-methyl-5-[[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]-1-piperidinecarboxamide	4.29
202		1-[[[4-Methyl-5-[[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]-amino]carbonyl]-3-piperidinecarboxylic acid ethyl ester	4.10
203		3,3-Dimethyl-N-[4-methyl-5-[[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]-1-piperidinecarboxamide	4.32
204		1-[[[4-Methyl-5-[[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]-amino]carbonyl]-4-piperidinecarboxylic acid ethyl ester	4.06
205		4-Methyl-2-[[[(3-methyl-2-pyridinyl)-amino]carbonyl]-amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.51

206		4-Methyl-2-[[[1-(phenylmethyl)-4-piperidinyl]amino]-carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazole-carboxamide	3.28
207		Octahydro-N-[4-methyl-5-[[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]-1(2H)-quinolinecarboxamide	4.55
208		3,4-Dihydro-N-[4-methyl-5-[[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]-2(1H)-isoquinolinecarboxamide	4.35
209		2-[[[(1,5-Dimethylhexyl)amino]carbonyl]-amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazole-carboxamide	4.72
210		4-Methyl-2-[[[(1-methylheptyl)amino]-carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazole-carboxamide	4.74
211		2-[[[(2-Fluorophenyl)methyl]amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.17

212		2-[[[[(2-Methoxyphenyl)methyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.22
213		2-[[[[(2-Ethoxyphenyl)methyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.36
214		2-[[[[(3-Methoxyphenyl)methyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.13
215		2-[[[[(4-Chlorophenyl)methyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.36
216		2-[[[[(4-Methoxyphenyl)methyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.12
217		2-[[[(2,2-Diphenylethyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.57
218		2-[[[(2-Aminoethyl)phenylamino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.70

219		2-[[[2-(3-Methoxyphenyl)ethyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.26
220		2-[[[2-(3,4-Dimethoxyphenyl)ethyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.05
221		2-[[[2-(4-Methoxyphenyl)ethyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.25
222		4-Methyl-2-[[[3-phenylpropyl]amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.40
223		2-[[[2-(Cyclohex-1-en-1-yl)ethyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.11
224		2-[[[4-(1,1-Dimethylethyl)cyclohexyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.85
225		2-[[[3-Butoxypropyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.33

226		2-[[[2-(2-Methoxyphenyl)ethyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.46
227		2-[[[2-(2-Chloro-4-fluorophenyl)methyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.39
228		2-[[[2-(Hexylmethylamino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.65
229		2-[[[2-(1-(4-Chlorophenyl)ethyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.42
230		2-[[[2-(3-Chlorophenyl)ethyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.44
231		4-Methyl-2-[[[2-(2-thienyl)ethyl]amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.18
232		2-[[[2-(2-Fluorophenyl)ethyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.85
233		4-Methyl-2-[[[2-(2-pyridinyloxy)ethyl]amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.28

234		2-[[[[(2-Bromo-4,5-dimethoxyphenyl)methyl]methylamino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.87
235		(E)-2-[[[(3,7-Dimethyl-2,6-octadienyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.34
236		2-[[[[(2,3-Dihydro-1,4-benzodioxin-2-yl)methyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.27

Examples 237 to 285

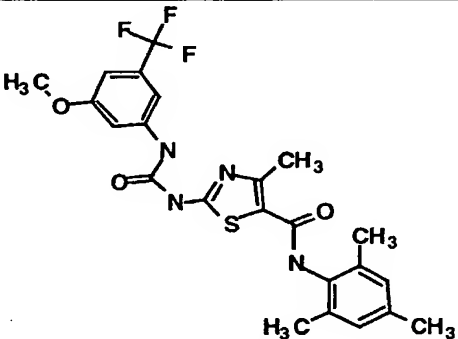
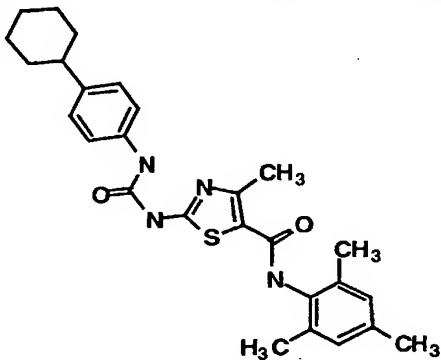
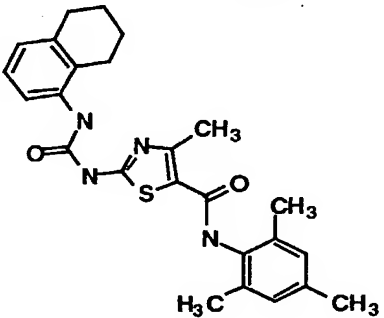
General Procedure

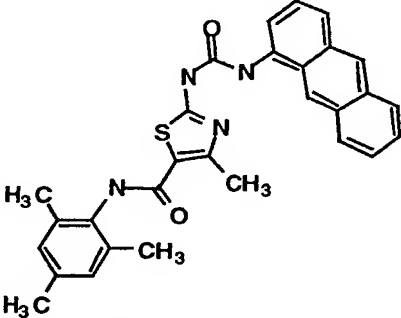
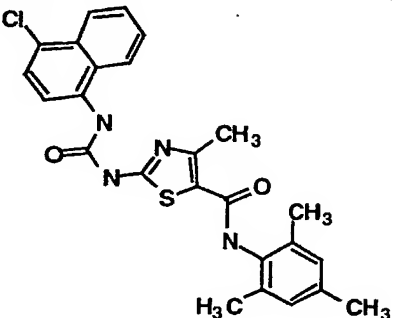
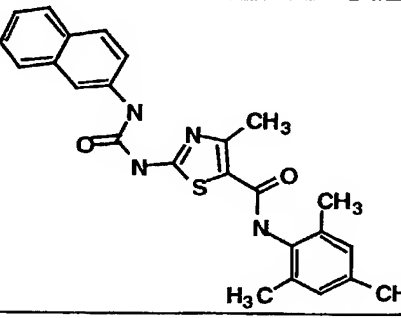
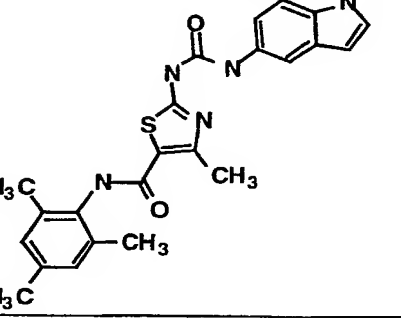
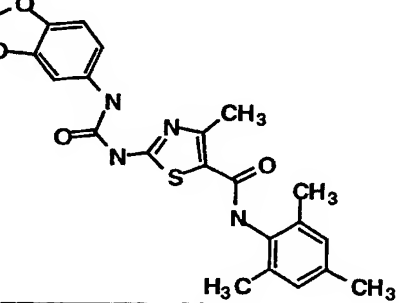
Compounds **237** to **285** were prepared following the procedure described below.

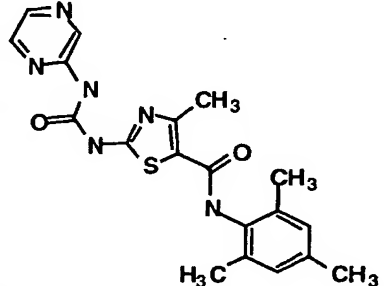
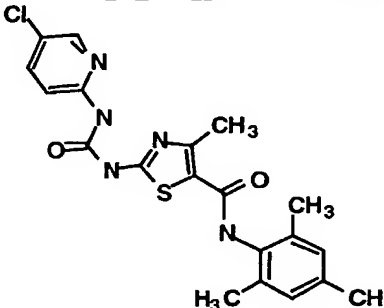
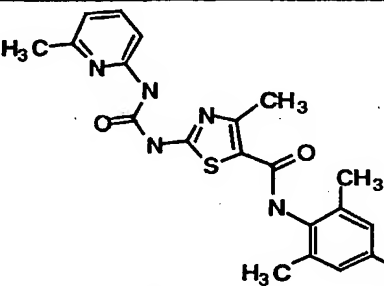
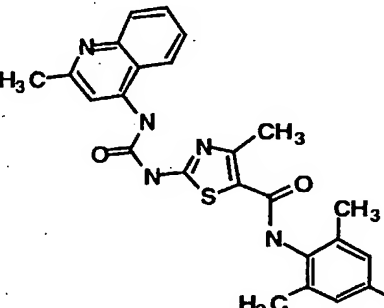
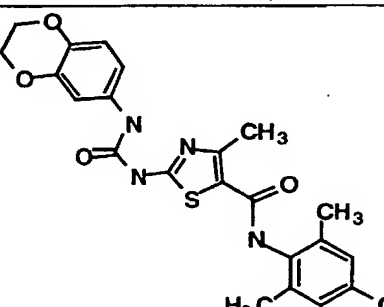
A solution of phenylcarbamate **181** (20 mg, 0.054 mmol) and the appropriate amine (0.08 mmol) in THF-acetonitrile (3 mL, 1:1) was stirred at rt overnight. The mixture was diluted with dichloromethane (4 mL) and washed with 1 N aq. HCl solution (1.5 mL, 2x), 1 N aq. NaOH solution (1.5 mL, 2x). The dichloromethane extract was separated, dried (MgSO₄), filtered and concentrated to obtain the title product.

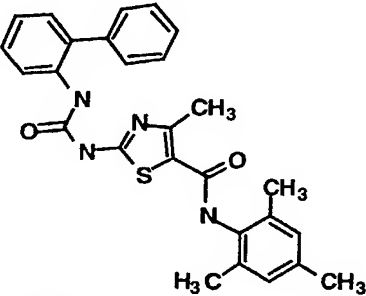
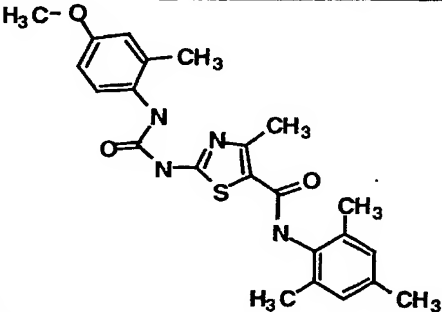
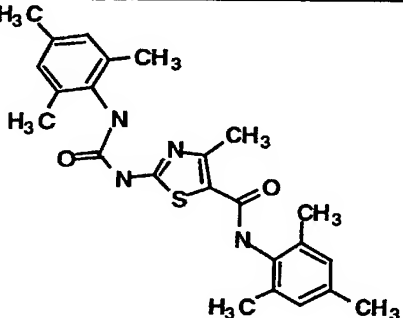
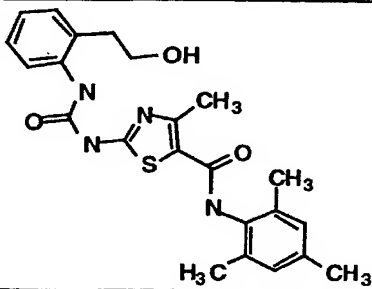
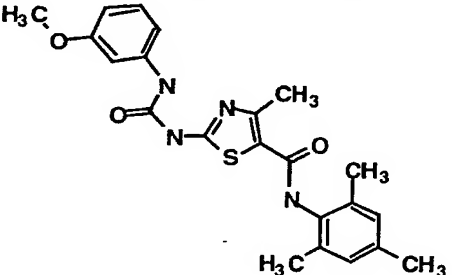
"HPLC Ret Time" is the HPLC retention time under the following conditions: For compounds **237-278** HPLC conditions are: YMC S5 ODS 4.6 x 50 mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H₂O, 0.2% H₃PO₄) to 100% solvent B (90% MeOH, 10% H₂O, 0.2% H₃PO₄), flow rate 4 mL/min, λ = 220 nM. For compounds **279-285** HPLC conditions are: Zorbax S8-C18 4.5 mm x 7.5 cm short

column, 8 min gradient starting from 100% solvent A (10% MeOH, 90% H₂O, 0.2% H₃PO₄) to 100% solvent B (90% MeOH, 10% H₂O, 0.2% H₃PO₄), flow rate 2.5 mL/min, λ = 217 nM.

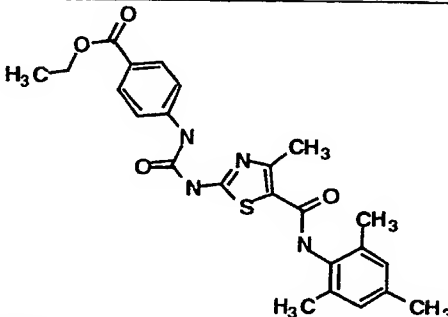
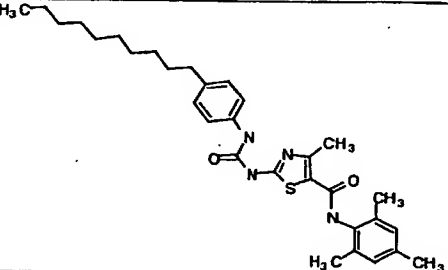
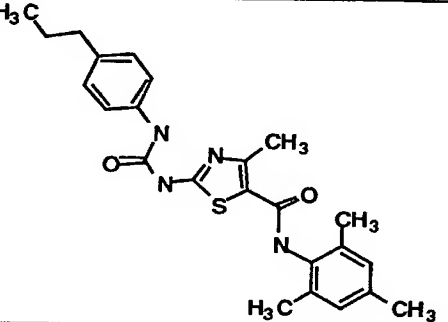
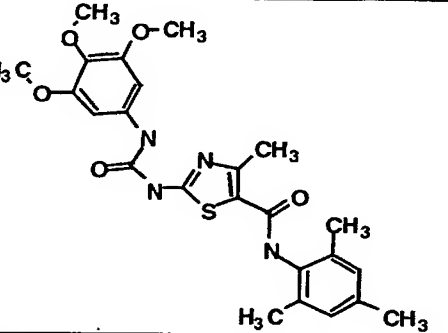
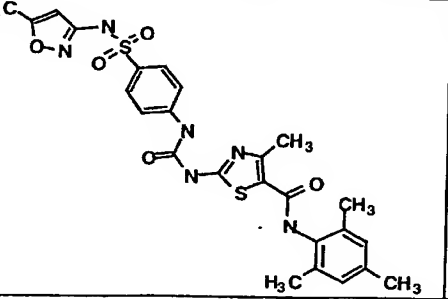
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
237		2-[[[3-Methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.36
238		2-[[[4-Cyclohexylphenyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.73
239		4-Methyl-2-[[[(5,6,7,8-tetrahydro-1-naphthalenyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.38

240		2-[[[(1-Anthracenylamino) carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.82
241		2-[[[(4-Chloro-1-naphthalenyl) amino] carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.76
242		4-Methyl-2-[[[(2-naphthalenylamino) carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.28
243		2-[[[(1H-Indol-5-ylamino) carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.00
244		2-[[[(1,3-Benzodioxol-5-ylamino) carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.76

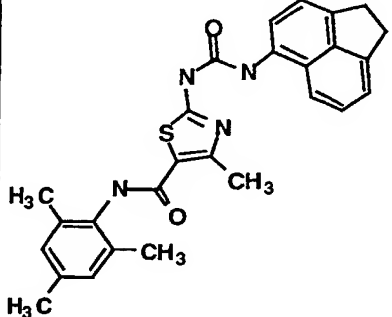
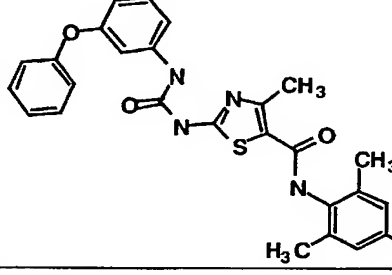
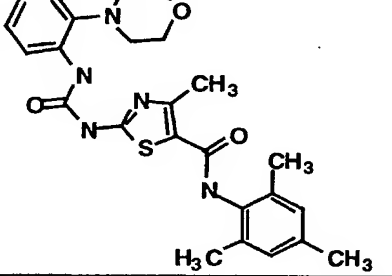
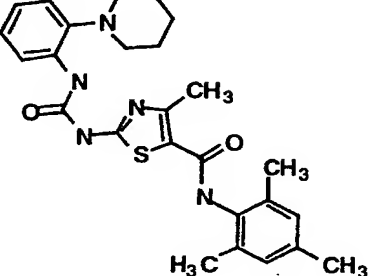
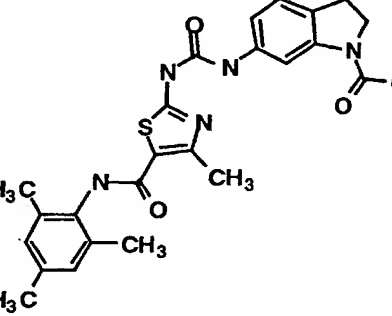
245		4-Methyl-2-[[[(2-pyrazinylamino)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.84
246		2-[[[(5-Chloro-2-pyridinyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.38
247		4-Methyl-2-[[[(6-methyl-2-pyridinyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.44
248		4-Methyl-2-[[[(2-methyl-4-quinolinyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.23
249		2-[[[(2,3-Dihydro-1,4-benzodioxin-6-yl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.72

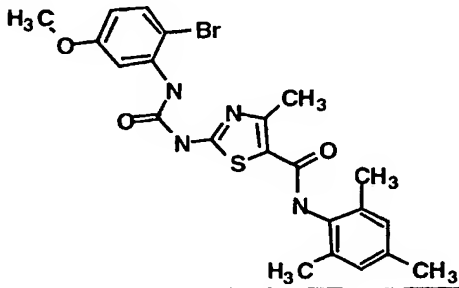
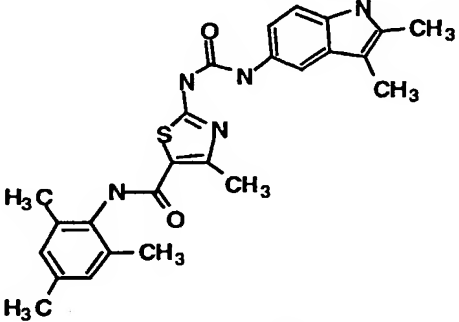
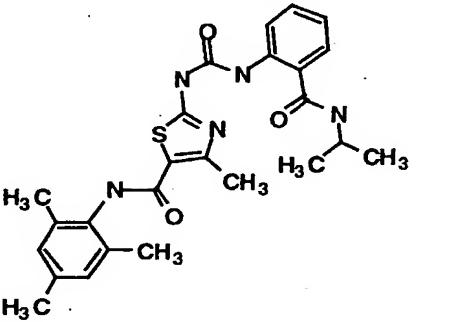
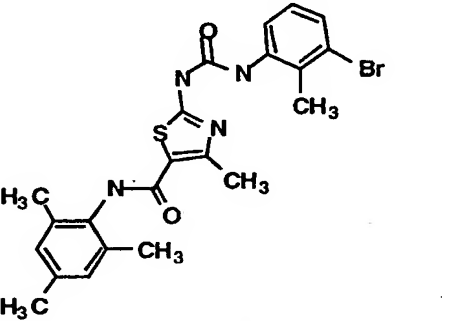
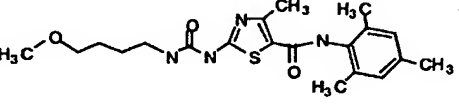
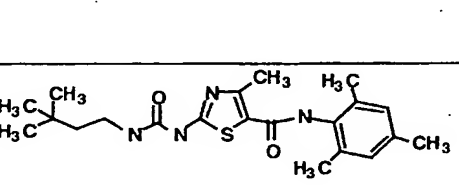
250		2-[[[([1,1'-Biphenyl]-2-ylamino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.29
251		2-[[[(4-Methoxy-2-methylphenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.80
252		4-Methyl-N-(2,4,6-trimethylphenyl)-2-[[[(2,4,6-trimethylphenyl)amino]carbonyl]amino]-5-thiazolecarboxamide	5.06
253		2-[[[2-(2-Hydroxyethyl)phenyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.02
254		2-[[[(3-Methoxyphenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.86

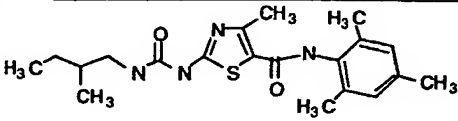
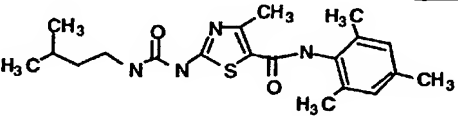
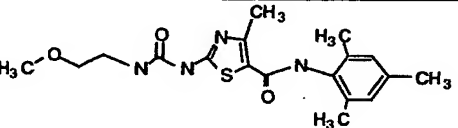
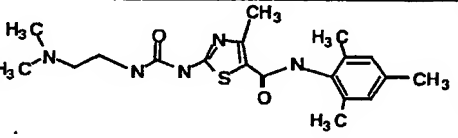
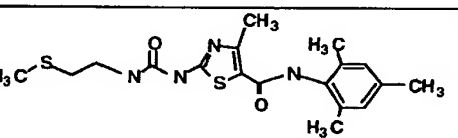
255		2-[[[(4-Methoxy[1,1'-biphenyl]-3-yl)amino]carbonyl]-4-amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.81
256		2-[[[(3-Acetylphenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.12
257		2-[[[(4-Cyanophenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.15
258		2-[[[(4-Fluoro-2-(trifluoromethyl)phenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.99
259		2-[[[(4-Hexyloxyphenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.42

260		4-[[[4-Methyl-5-[[[(2,4,6-trimethylphenyl) amino]carbonyl]-2-thiazolyl]-amino]carbonyl]amino]benzoic acid ethyl ester	4.26
261		2-[[[(4-Decylphenyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	
262		4-Methyl-2-[[[(4-propylphenyl) amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.71
263		4-Methyl-2-[[[(3,4,5-trimethoxyphenyl) amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.67
264		4-Methyl-2-[[[[4-[[[(5-methyl-3-isoxazolyl) amino]sulfonyl]phenyl]amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.27

265		4-[[[4-Methyl-5-[[2,4,6-trimethylphenyl]amino]carbonyl]-2-thiazolyl]-amino]carbonyl]-amino]-benzoic acid butyl ester	4.75
266		2-[[[1-Isoquinolinyl amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.81
267		4-Methyl-2-[[[2-[(phenyl-methyl)thio]-phenyl]amino]carbonyl]-amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.42
268		4-Methyl-2-[[[4-[(5-phenoxy-pentyl)oxy]phenyl]amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.96
269		2-[[[5-(1,1-Dimethyl-propyl)-2-methoxy-phenyl]amino]carbonyl]-amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.76

270		2-[[[(1,2-Dihydro-5-acenaphthylenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.70
271		4-Methyl-2-[[[(3-phenoxyphenyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.70
272		4-Methyl-2-[[[2-(4-morpholinyl)phenyl]amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.01
273		4-Methyl-2-[[[2-(1-piperidinyl)phenyl]amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.55
274		2-[[[(1-Acetyl-2,3-dihydro-1H-indol-6-yl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.08

275		2-[[[(2-Bromo-5-methoxyphenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.55
276		2-[[[(2,3-Dimethyl-1H-indol-5-yl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.30
277		4-Methyl-2-[[[(2-[[[(1-methylethyl)amino]carbonyl]phenyl]amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.82
278		2-[[[(3-Bromo-2-methylphenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.60
279		2-[[[(4-Methoxybutyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	7.62
280		2-[[[(3,3-Dimethylbutyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	9.13

281		4-Methyl-2-[[[(2-methylbutyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.90
282		4-Methyl-2-[[[(3-methylbutyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.98
283		2-[[[(2-Methoxyethyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	7.30
284		2-[[[2-(Dimethylamino)ethyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.73
285		4-Methyl-2-[[[2-(methylthio)ethyl]amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.19

Examples 286 to 311

General Procedure

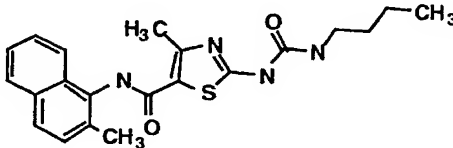
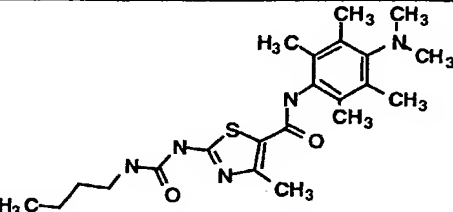
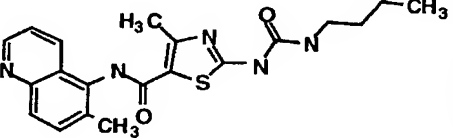
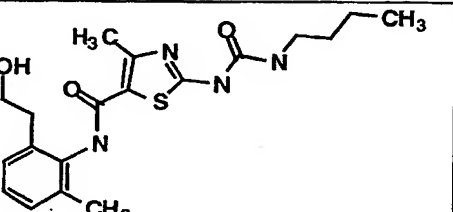
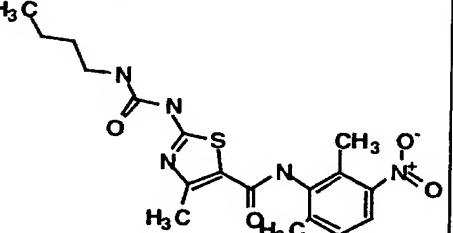
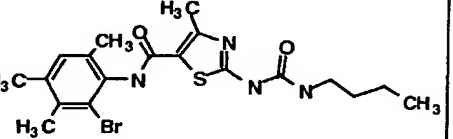
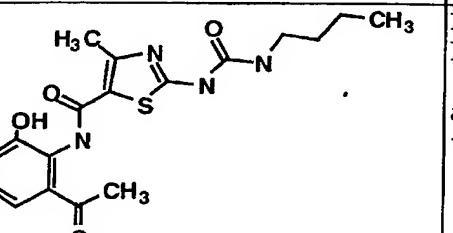
- Compounds **286** to **311** with the exception of compound **307** were prepared following the procedure described below.
- A solution of 2-[[[(Butylamino)carbonyl]amino]-4-methyl-5-thiazole carboxylic acid chloride (30 mg, 0.11 mmol), appropriate amine (0.12 mmol) in THF (1 mL) was treated with diisopropylethyl amine (22.6 μ L, 0.13 mmol). The mixture was purged with argon and stirred mechanically in a vial for 22 h, diluted with dichloromethane (4 mL) and washed with 2 N aq. HCl solution (3x). The organic extract was separated, dried (Na_2SO_4), filtered and concentrated. The crude products were purified either by truturation with dichloromethane-ether (1:1) or by silica gel

chromatography (elution solvent: 80% EtOAc in hexanes followed by EtOAc) or by automatic preparative HPLC (conditions: YMC S5 ODS A 20 x 100 mm Column, 10 min gradient starting from 30% solvent B (90% MeOH, 10% H₂O, 0.1% TFA) and 70% solvent A (10% MeOH, 90% H₂O, 0.1% TFA) to 100% solvent B, flow rate 20 mL/min, λ = 220 nM.

Compound **307** was prepared following the procedure described below. A suspension solution of 2-[[[(Butylamino)carbonyl]amino]-4-methyl-5-thiazole carboxylic acid (100 mg, 0.36 mmol), and HATU (170 mg, 0.44 mmol) in DMF (3 mL) was treated with diisopropylethyl amine (62 mL, 0.44 mmol). The mixture was heated to 60°C for 2 h, cooled, diluted with dichloromethane (12 mL), washed with 8M aq. Urea solution in 2 N aq. HCl (6 mL, 3x), 5% aq. KHCO₃ solution (6 mL, 3x), dried (Na₂SO₄), filtered and concentrated. The residue was triturated with EtOAc-ether to obtain the mixed anhydride intermediate (102 mg, 74%) as a white solid. A 1 M solution of sodium bis(trimethylsilylamide) in THF (170 μ L, 0.17 mmol) was added dropwise to a stirred solution of 2,6-dichloroaniline (19.4 mg, 0.12 mmol) in THF (1 mL). After 15 min, the mixed anhydride intermediate (41.3 mg, 0.11 mmol) was added in one portion. A few drops of DMF was added and the solution was stirred for 16 h. Additional 1 M solution of sodium bis(trimethylsilylamide) (110 μ L) was added and the mixture was stirred for additional 2 h. The mixture was diluted with dichloromethane (4 mL) and washed with 2 N aq. HCl solution (2 mL, 3x), satd. aq. KHCO₃ solution (3x), dried (Na₂SO₄), filtered and concentrated. The solid was washed with hexanes (2x) and the residue was chromatographed on a silica gel column. Elution with 80% EtOAc in hexanes followed by EtOAc afforded **307** (12 mg, 27%) as a light tan solid. "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 50 mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H₂O, 0.2% H₃PO₄) to 100% solvent B (90% MeOH, 10% H₂O, 0.2% H₃PO₄), flow rate 4 mL/min, λ = 220 nM.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
286		2-[[[(Butylamino)carbonyl]amino]-N-(2,3-dihydro-1H-inden-5-yl)-4-methyl-5-thiazole-carboxamide	4.20
287		2-[[[(Butylamino)carbonyl]amino]-N-2-naphthalenyl-4-methyl-5-thiazolecarboxamide	4.20
288		2-[[[(Butylamino)carbonyl]amino]-N-(3-hydroxy-2-naphthalenyl)-4-methyl-5-thiazolecarboxamide	4.24
289		2-[[[(Butylamino)carbonyl]amino]-N-(2-fluoro-5-methylphenyl)-4-methyl-5-thiazolecarboxamide	3.95
290		2-[[[(Butylamino)carbonyl]amino]-N-(2,6-dimethylphenyl)-4-methyl-5-thiazolecarboxamide	3.78
291		N-(4-Bromo-2-methylphenyl)-2-[[[(butylamino)carbonyl]amino]-4-methyl-5-thiazolecarboxamide	4.12

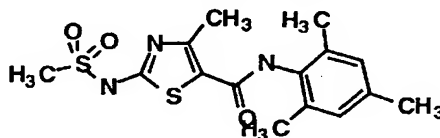
292		N-(3-Bromo-2,4,6-trimethylphenyl)-2-[[[(butylamino)carbonyl]amino]-4-methyl-5-thiazolecarboxamide	4.28
293		2-[[[(butylamino)carbonyl]amino]-N-[2,6-dimethyl-3-(1-methylethyl)phenyl]-4-methyl-5-thiazolecarboxamide	4.28
294		N-(2-Bromo-4,6-dimethylphenyl)-2-[[[(butylamino)carbonyl]amino]-4-methyl-5-thiazolecarboxamide	4.00
295		3-[[[2-[[[(butylamino)carbonyl]amino]-4-methyl-5-thiazolyl]-carbonyl]amino]-4-methyl-2-thiophene-carboxylic acid methyl ester	3.83
296		2-[[[(butylamino)carbonyl]amino]-4-methyl-N-(2-methyl-6-quinolinyl)-5-thiazolecarboxamide	2.98
297		2-[[[(butylamino)carbonyl]amino]-N-(2,6-dimethoxyphenyl)-4-methyl-5-thiazolecarboxamide	3.39
298		2-[[[(butylamino)carbonyl]amino]-N-(4-methoxy-2-naphthalenyl)-4-methyl-5-thiazolecarboxamide	4.31

299		2-[[[(Butylamino) carbonyl] amino]-N-(2-methyl-1-naphthalenyl)-4-methyl-5-thiazole-carboxamide	3.92
300		2-[[[(Butylamino) carbonyl] amino]-N-[4-(dimethylamino)-2,3,5,6-tetramethylphenyl]-4-methyl-5-thiazolecarboxamide	3.14
301		2-[[[(Butylamino) carbonyl] amino]-N-(6-methyl-5-quinolinyl)-4-methyl-5-thiazolecarboxamide	3.13
302		2-[[[(Butylamino) carbonyl] amino]-N-[2-(2-hydroxyethyl)-6-methylphenyl]-4-methyl-5-thiazolecarboxamide	3.50
303		2-[[[(Butylamino) carbonyl] amino]-N-(2,6-dimethyl-3-nitrophenyl)-4-methyl-5-thiazolecarboxamide	3.75
304		N-(2-Bromo-3,4,6-trimethylphenyl)-2-[[[(butylamino) carbonyl] amino]-4-methyl-5-thiazolecarboxamide	4.12
305		N-(2-Acetyl-6-hydroxyphenyl)-2-[[[(butylamino) carbonyl] amino]-4-methyl-5-thiazolecarboxamide	3.75

306		[4-[[[2-[[[(Butylamino)carbonyl]amino]-4-methyl-5-thiazolyl]-carbonyl]amino]-2,3,5,6-tetramethylphenyl]carbamic acid 1,1-dimethylethyl ester	4.10
307		2-[[[(Butylamino)carbonyl]amino]-N-(2,6-dichlorophenyl)-4-methyl-5-thiazolecarboxamide	4.42
308		N-(4-Amino-2,3,5,6-tetramethylphenyl)-2-[[[(butylamino)carbonyl]amino]-4-methyl-5-thiazolecarboxamide	3.15
309		N-[5-(Acetylamino)-2,4-dimethylphenyl]-2-[[[(butylamino)carbonyl]amino]-4-methyl-5-thiazolecarboxamide	3.52
310		N-(4-Bromo-2,6-dimethylphenyl)-2-[[[(butylamino)carbonyl]amino]-4-methyl-5-thiazolecarboxamide	4.93
311		2-[[[(Butylamino)carbonyl]amino]-N-(2-chloro-6-methylphenyl)-4-methyl-5-thiazolecarboxamide	4.51

Example 312

Preparation of 4-Methyl-2-[(methanesulfonyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



A. Ethyl-2-[(methylsulfonyl)amino]-4-methyl-thiazole-5-carboxylate

A stirred solution of ethyl-2-amino-4-methyl-thiazole-5-carboxylate (558 mg, 3 mmol) in dichloromethane (15 mL) and pyridine (5 mL) was treated with methanesulfonyl chloride (687 mg, 6 mmol) at rt overnight. The
5 solution was diluted with dichloromethane (50 mL) and washed with 2N aq. HCl solution (15 mL, 3x), dried (MgSO₄), filtered and concentrated. The crude residue was diluted with ether (25 mL) and the solid was filtered, washed with 1:1 ether:hexane mixture (10 mL, 3x), and dried *in vacuo* to obtain the title compound (687 mg, 87%) as an off-white solid.

10

B. 2-[(Methylsulfonyl)amino]-4-methyl-thiazole-5-carboxylic acid

A stirred solution of Ethyl-2-[(methylsulfonyl)amino]-4-methyl-thiazole-5-carboxylate (300 mg, 1.14 mmol) in methanol (9 mL) was treated with a 1N NaOH solution (28.4 mL, 28.4 mmol). The mixture was stirred at rt
15 overnight. The solution was cooled to 0 °C and acidified with 6N aq. HCl solution to pH 1. The solution was extracted with dichloromethane-chloroform mixture. The organic extract was dried (MgSO₄), filtered and concentrated *in vacuo* to obtain the title acid (148 mg, 55%).

20 C.4-Methyl-2-[(methylsulfonyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide

Diisopropylethylamine (87 µL, 0.5 mmol) was added to a solution of **312 B** (99 mg, 0.42 mmol), 2,4,6-trimethylaniline (68 µL, 0.5 mmol), and [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium]hexafluorophosphate
25 (HATU, 191 mg, 0.5 mmol) in DMF (3 mL). The mixture was stirred at rt overnight, diluted with EtOAc and washed with 0.5 N aq. HCl solution (15 mL), 10% aq. LiCl solution (25 mL, 3x), water (930 mL, 2x), brine, dried (MgSO₄), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 50% EtOAc in hexanes, followed by

75% EtOAc in hexanes and 2% MeOH in EtOAc to obtain the title compound (19 mg, 13%) as a white solid.

Example 313

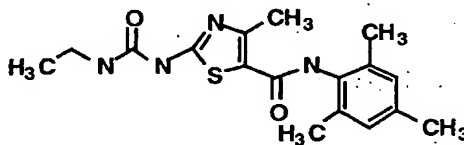
5 Preparation of 4-Methyl-2-[[[(phenylamino)thiocarbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



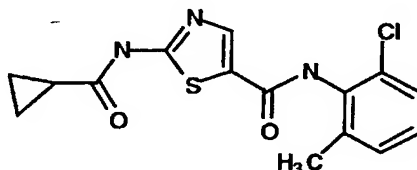
10 A solution of 2 (45 mg, 0.16 mmol) and phenylisothiocyanate (43 mg, 0.32 mmol) in pyridine (2 mL) was heated to 80°C for 20 h. The mixture was cooled, diluted with dichloromethane-THF mixture (80 mL, 3:1) and washed with 2 N aq. HCl solution (15 mL, 2x). The organic extract was dried (MgSO₄), filtered and concentrated. The residue was diluted with EtOAc (20 mL) and the solid was filtered, washed with ether (10 mL, 3x),
15 and dried *in vacuo* to obtain the title compound (35 mg, 52%) as an off-white solid.

Example 314

20 Preparation of 2-[[[(Ethylamino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



Compound 314 was prepared by an analogous method as that of compounds 171-180, using ethylisocyanate to give the title compound 314
25 as a white solid (65%).

Example 315Preparation of N-(2-Chloro-6-methylphenyl)-2-
[(cyclopropylcarbonyl)amino]-5-thiazolecarboxamide

5

A. Ethyl-2-tert-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylate

A suspension of ethyl-2-amino-thiazole-5-carboxylate (972 mg, 6 mmol, B. Plouvrier, C. Bailly, R. Houssin, J.-P. Henlchart *Heterocycles* 32(4), 693-701, 1991 and H. J. Becker, *J. de Jonge Rec. Trav. Chim.*, 61, 463, 1942), di-
10 butyldicarbonate (1.94 g, 9 mmol) and 4-dimethylaminopyridine (73 mg, 0.6 mmol) in dry tetrahydrofuran (75 mL) was stirred under nitrogen for 24 h. The solvent was evaporated *in vacuo*. The residue was suspended in ether (50 mL). The solid was washed with ether (10 mL, 3x), and dried *in*
15 *vacuo* to obtain the title compound (1.1 g, 70%).

B. 2-tert-butoxycarbonyloxyamino-thiazole-5-carboxylic acid

A stirred solution of ethyl-2-tert-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylate (1.1 g, 4.2 mmol) in tetrahydrofuran-methanol (80
20 mL, 1:1) was treated with a 6N aq. NaOH solution (20 mL, 120 mmol). The mixture was stirred at rt for 24 h. Most of THF and methanol were removed by distillation under reduced pressure and the aq. Solution was acidified with 6 N aq. HCl solution (22 mL). The precipitated solid was filtered, washed with water and ether, air dried followed by drying *in*
25 *vacuo* to obtain the title acid (940 mg, 96%) as an off-white solid.

C. [5-[[[(2-chloro-6-methylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

A 2 M solution of oxalyl chloride in dichloromethane (1 mL, 2 mmol) was added dropwise to a stirred solution of 2-*tert*-butoxycarbonyloxyamino-thiazole-5-carboxylic acid (234 mg, 1 mmol) in THF (10 mL) and N,N-dimethyl formamide (few drops). The solution was stirred at rt for 4 h. The solvent was evaporated under reduced pressure, and *in vacuo* to obtain the crude acid chloride.

2-Chloro-6-methyl aniline (212 mg, 1.5 mmol) was added dropwise to a stirred solution of crude 2-*tert*-butoxycarbonyloxyamino-thiazole-5-carboxylic acid chloride (1 mmol) in dichloromethane (10 mL) at 0°C. Diisopropylethylamine (516 mg, 4 mmol) was added. The solution was allowed to warm to rt and stirred for 24 h, diluted with dichloromethane (60 mL) and washed with 2 N aq. HCl solution (15 mL). The organic extract was dried (MgSO₄), filtered and concentrated. The residue was diluted with EtOAc-ether (25 mL, 1:4) and the solid was filtered and washed with ether (5 mL, 4x), and dried *in vacuo* to obtain the title compound (175 mg, 48%) as a tan solid.

20 D. 2-Amino-N-(2-chloro-6-methylphenyl)- 5-thiazolecarboxamide

Compound **315D** was prepared by an analogous method as that of **2**, except using compound **315C** to give the title compound **315D** as a tan solid.

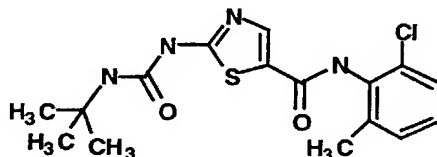
25 E. 2-[(Cyclopropylcarbonyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide

A solution of **315D** (50.6 mg, 0.19 mmol) and cyclopropanecarboxylic acid anhydride (302 mg, 1.96 mmol) in dioxane (2 mL) was heated to 93 °C overnight. The mixture was concentrated *in vacuo*, diluted with EtOAc and washed with satd. aq. KHCO₃ solution (2x). The organic extract was

dried (Na_2SO_4), filtered and concentrated. The residue was triturated with ether to obtain the title compound (11 mg, 17%) as a white solid.

Example 316

5 Preparation of 2-[[[(1,1-Dimethylethyl)amino]carbonyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide

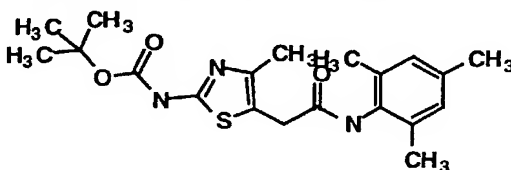


Sodium hydride (19.2 mg, 0.8 mmol) was added to a solution of 315D (48.3 mg, 0.18 mmol) and t-butyliisocyanate (41 μL , 0.36 mmol) in THF (5 mL) at 0 °C. After 1 h, the mixture was diluted with EtOAc and washed with cold satd. aq. ammonium chloride solution. The aqueous layer was separated and extracted with EtOAc. The EtOAc extracts were combined, dried (Na_2SO_4), filtered and concentrated. The residue was purified by automatic preparative HPLC (conditions: YMC S5 ODS A 20 x 100 mm Column, 10 min gradient starting from 10% solvent B (90% MeOH, 10% H₂O, 0.1% TFA) and 90% solvent A (10% MeOH, 90% H₂O, 0.1% TFA) to 100% solvent B, flow rate 20 mL/min, λ = 220 nm to obtain the title compound (18 mg, 28%) as an off-white solid.

20

Example 317

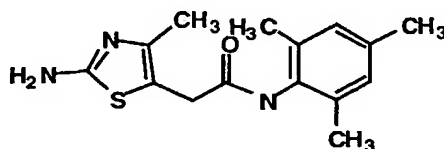
Preparation of 2-[[[(1,1-Dimethylethoxy)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazoleacetamide



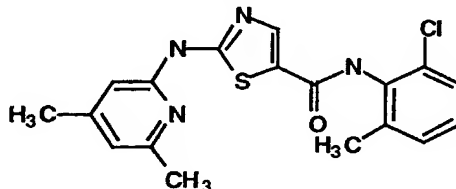
25

Compound **317** was prepared by an analogous method as that of **1**, except using methyl-2-amino-4-methyl-thiazole-5-acetate to give the title compound **317** as an off-white solid.

5

Example 318Preparation of 2-Amino-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazoleacetamide

- 10 Compound **318** was prepared by an analogous method as that of **2**, except using **317** to give the title compound **318** as a light brown solid.

Example 319Preparation of N-(2-Chloro-6-methylphenyl)-2-[(4,6-dimethyl-2-pyridinyl)amino]-5-thiazolecarboxamide

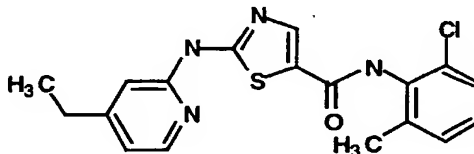
5

A. 2-Bromo-N-(2-chloro-6-methylphenyl)- 5-thiazolecarboxamide

A solution of copper (II) bromide (2.68 g, 12 mmol) in acetonitrile (50 mL) was purged with nitrogen and cooled to 0 °C. t-Butyl nitrite (2 mL, 15 mmol) was added, followed by a solution of compound **315D** (2.68 g, 10 mmol) in acetonitrile (50 mL). The mixture was stirred at rt overnight and concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with satd. aq. NaHCO₃ solution and the precipitate was removed by filtration. The organic extract was dried (Na₂SO₄), filtered and concentrated. The residue was crystallized from EtOAc/ether/hexanes mixture to obtain the title compound (1.68 g, 51%) as a yellow solid.

B. N-(2-Chloro-6-methylphenyl)-2-[(4,6-dimethyl-2-pyridinyl)amino]-5-thiazolecarboxamide

95% Sodium hydride (15 mg) was added to a mixture of **319A** (25 mg, 0.075 mmol) and 4,6-dimethyl-2-aminopyridine (37 mg, 0.302 mmol) in THF (1 mL). The mixture was heated to 60 °C overnight, cooled to rt and diluted with satd. aq. ammonium chloride solution. The mixture was extracted with EtOAc (2x). Organic extracts were combined, washed with water and dried (Na₂SO₄), filtered and concentrated. The residue was triturated with ether to obtain the title compound (17.5 mg, 63%) as a tan solid.

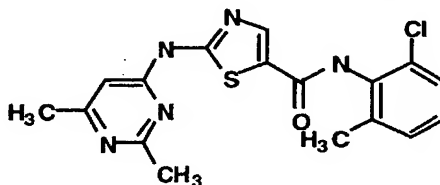
Example 320Preparation of N-(2-Chloro-6-methylphenyl)-2-[(4-ethyl-2-pyridinyl)amino]-5-thiazolecarboxamide

5

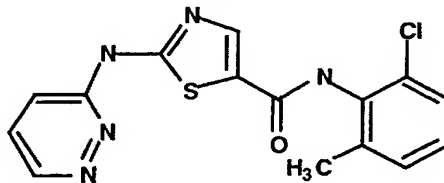
Compound **320** was prepared by an analogous method as that of **319B**, except using 4-ethyl-2-aminopyridine to give the title compound **320**.

Example 321

10 Preparation of N-(2-Chloro-6-methylphenyl)-2-[(2,6-dimethyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide



Compound **321** was prepared by an analogous method as that of **319B**,
15 except using 2,6-dimethyl-4-aminopyrimidine to give the title compound **321**.

Example 322Preparation of N-(2-Chloro-6-methylphenyl)-2-(3-pyridazinylamino)-5-thiazolecarboxamide

5

Compound **322** was prepared by an analogous method as that of **319B**, except using 3-aminopyridazine to give the title compound **322**.

Examples 323 to 33510 *General Procedure*

Compounds **323** to **335** were prepared following the procedure described below. Diisopropylethyl amine (60 μ L, 0.34 mmol) was added to a mixture of amine **144** (31 mg, 0.11 mmol), appropriate carboxylic acid (0.13 mmol), 1-hydroxy-7-azabenzotriazole (19.5 mg, 0.14 mmol), and ethyl-3-(3-
15 dimethylamino)-propyl carbodiimide hydrochloride (26.8 mg, 0.14 mmol) in THF (0.4 mL). The mixture was heated in a sealed tube under argon at 50 $^{\circ}$ C for 24 h. The reaction mixture was diluted with dichloromethane (4 mL) and washed with 1 N aq. HCl solution. The dichloromethane solution was passed through a Varian Mega Bond Elut SCX cation exchange
20 column (prewashed with methanol and equilibrated with acetonitrile-methanol (4:1). The column was eluted sequentially with acetonitrile-methanol (4:1), methanol-2M methanolic ammonia (4:1). Fractions containing the product were combined and concentrated in vacuo. "HPLC Ret Time" is the HPLC retention time under the following
25 conditions: YMC S5 ODS 4.6 x 50 mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H₂O, 0.2% H₃PO₄) to

100% solvent B (90% MeOH, 10% H₂O, 0.2% H₃PO₄), flow rate 4 mL/min,
 $\lambda = 220$ nm.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
323		N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(2-thienylcarbonyl)amino]-5-thiazolecarboxamide	3.70
324		N-(2-Chloro-6-methylphenyl)-2-[(cyclopropylcarbonyl)amino]-4-methyl-5-thiazolecarboxamide	3.41
325		N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(2-furanylcarbonyl)amino]-5-thiazolecarboxamide	3.49
326		N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(3-thienylcarbonyl)amino]-5-thiazolecarboxamide	3.71
327		N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(3-furanylcarbonyl)amino]-5-thiazolecarboxamide	3.57
328		trans-N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(2-phenylcyclopropylcarbonyl)amino]-5-thiazolecarboxamide	4.09
329		N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(2-methylcyclopropylcarbonyl)amino]-5-thiazolecarboxamide	3.65
330		N-(2-Chloro-6-methylphenyl)-2-[(cyclobutylcarbonyl)amino]-4-methyl-5-thiazolecarboxamide	3.63

331		N N-(2-Chloro-6-methylphenyl)-2-[(cyclopentylcarbonyl)amino]-4-methyl-5-thiazolecarboxamide	3.82
332		N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(2-methyl-1-oxopropyl)amino]-5-thiazolecarboxamide	3.50
333		N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(1-oxopentyl)amino]-5-thiazolecarboxamide	3.79
334		N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(2-methyl-1-oxopentyl)amino]-5-thiazolecarboxamide	3.90
335		2-(Benzoylamino)-N-(2-chloro-6-methylphenyl)-4-methyl-5-thiazolecarboxamide	3.79

Examples 336 to 362

General Procedure

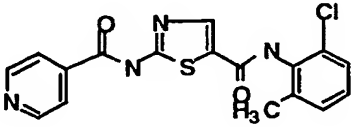
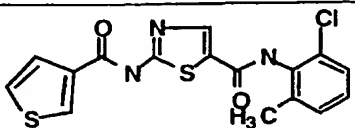
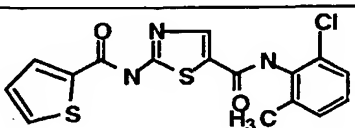
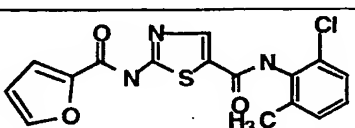
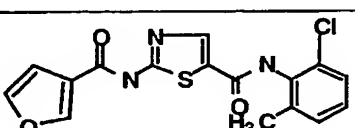
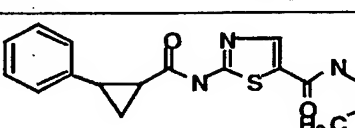
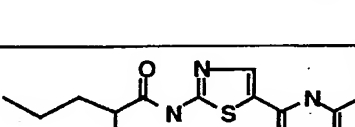
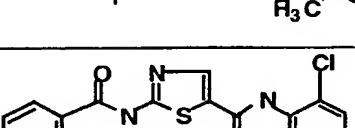
- 5 Compounds **336** to **362** were prepared by an analogous method as that of **323-335**, except using **315D** in place of **144**. The crude products were purified by automatic preparative HPLC (conditions: YMC S5 ODS A 20 x 100 mm Column, 10 min gradient starting from 10% solvent B (90% MeOH, 10% H₂O, 0.1% TFA) and 90% solvent A (10% MeOH, 90% H₂O,
- 10 0.1% TFA) to 100% solvent B, flow rate 20 mL/min, λ = 220 nM to obtain the title compounds **336-362**.

“HPLC Ret Time” is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 50 mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H₂O, 0.2% H₃PO₄) to

15 100% solvent B (90% MeOH, 10% H₂O, 0.2% H₃PO₄), flow rate 4 mL/min, λ = 220 nM.

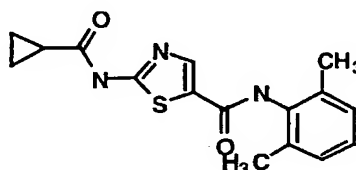
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
336		N-(2-Chloro-6-methylphenyl)-2-[(1-oxopropyl)amino]-5-thiazolecarboxamide	3.53
337		N-(2-Chloro-6-methylphenyl)-2-[(1-oxobutyl)amino]-5-thiazolecarboxamide	3.61
338		N-(2-Chloro-6-methylphenyl)-2-[(2-ethyl-1-oxobutyl)amino]-5-thiazolecarboxamide	3.54
339		N-(2-Chloro-6-methylphenyl)-2-[[1-(phenylcyclopropyl)carbonyl]amino]-5-thiazolecarboxamide	3.86
340		N-(2-Chloro-6-methylphenyl)-2-[[1-(1-methylcyclopropyl)carbonyl]amino]-5-thiazolecarboxamide	3.53
341		N-(2-Chloro-6-methylphenyl)-2-[[1-(2,2-dichloro-1-methylcyclopropyl)carbonyl]amino]-5-thiazolecarboxamide	3.53
342		N-(2-Chloro-6-methylphenyl)-2-[[1-(2-methylcyclopropyl)carbonyl]amino]-5-thiazolecarboxamide	3.53
343		N-(2-Chloro-6-methylphenyl)-2-[[1-(1-hydroxycyclopropyl)carbonyl]amino]-5-thiazolecarboxamide	3.58
344		N-(2-Chloro-6-methylphenyl)-2-[[1-(2,2,3,3-tetramethylcyclopropyl)carbonyl]amino]-5-thiazolecarboxamide	3.69

345		N-(2-Chloro-6-methylphenyl)-2-[[1-(1-cyanocyclopropyl)-carbonyl]amino]-5-thiazolecarboxamide	3.53
346		N-(2-Chloro-6-methylphenyl)-2-[(cyclobutylcarbonyl)amino]-5-thiazolecarboxamide	3.52
347		N-(2-Chloro-6-methylphenyl)-2-[(cyclopentylcarbonyl)amino]-5-thiazolecarboxamide	3.59
348		N-(2-Chloro-6-methylphenyl)-2-[(cyclohexylcarbonyl)amino]-5-thiazolecarboxamide	3.78
349		N-(2-Chloro-6-methylphenyl)-2-[(phenylacetyl)amino]-5-thiazolecarboxamide	3.62
350		N-(2-Chloro-6-methylphenyl)-2-[(cyclohexylacetyl)amino]-5-thiazolecarboxamide	4.07
351		N-(2-Chloro-6-methylphenyl)-2-[(4-pyridinylacetyl)amino]-5-thiazolecarboxamide	3.75
352		N-(2-Chloro-6-methylphenyl)-2-[[2,5-dimethyl-1H-pyrrol-3-yl]carbonyl]amino]-5-thiazolecarboxamide	3.17
353		N-(2-Chloro-6-methylphenyl)-2-[(2-pyridinylcarbonyl)amino]-5-thiazolecarboxamide	3.07
354		N-(2-Chloro-6-methylphenyl)-2-[(3-pyridinylcarbonyl)amino]-5-thiazolecarboxamide	3.07

355		N-(2-Chloro-6-methylphenyl)-2-[(4-pyridinylcarbonyl)amino]-5-thiazolecarboxamide	3.61
356		N-(2-Chloro-6-methylphenyl)-2-[(3-thienylcarbonyl)amino]-5-thiazolecarboxamide	3.60
357		N-(2-Chloro-6-methylphenyl)-2-[(2-thienylcarbonyl)amino]-5-thiazolecarboxamide	3.61
358		N-(2-Chloro-6-methylphenyl)-2-[(2-furanylcarbonyl)amino]-5-thiazolecarboxamide	3.61
359		N-(2-Chloro-6-methylphenyl)-2-[(3-furanylcarbonyl)amino]-5-thiazolecarboxamide	3.69
360		trans-N-(2-Chloro-6-methylphenyl)-2-[[[(2-phenylcyclopropyl)carbonyl]amino]-5-thiazolecarboxamide	3.98
361		N-(2-Chloro-6-methylphenyl)-2-[(2-methyl-1-oxopentyl)amino]-5-thiazolecarboxamide	3.90
362		2-(Benzoylamino)-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	3.61

Example 363

Preparation of 2-[(Cyclopropylcarbonyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide

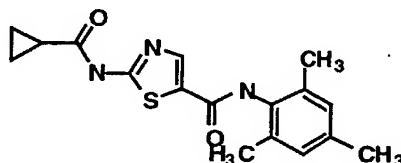


Compound **363** was prepared by an analogous method as that of **315**, except using 2,6-dimethylaniline to give the title compound **363**.

5

Example 364

Preparation of 2-[(Cyclopropylcarbonyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide

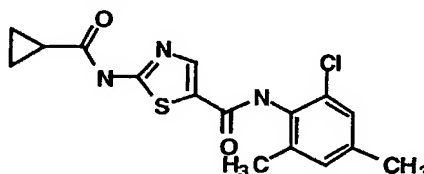


10 Compound **364** was prepared by an analogous method as that of **315**, except using 2,4,6-trimethylaniline to give the title compound **364**.

Example 365

Preparation of N-(2-Chloro-4,6-dimethylphenyl)-2-[(cyclopropylcarbonyl)amino]-5-thiazolecarboxamide

15

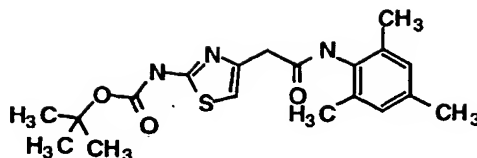


Compound **365** was prepared by an analogous method as that of **315**, except using 2-chloro-4,6-dimethylaniline to give the title compound **365**.

20

Example 366

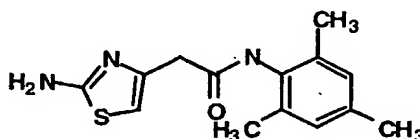
Preparation of [4-[2-Oxo-2-[(2,4,6-trimethylphenyl)amino]ethyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester



Compound **366** was prepared by an analogous method as that of **1** except, using 2-*tert*-butoxycarbonyloxyamino-thiazole-4-acetic acid to give the title
 5 compound **366** as a white solid.

Example 367

Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-4-thiazoleacetamide



10

Compound **367** was prepared by an analogous method as that of **4**, except using **365** to give the title compound **367** as a white solid.

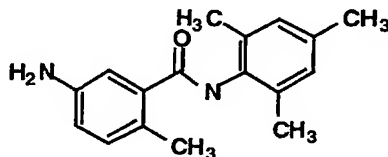
Example 368

Preparation of 2-Methyl-5-nitro-N-(2,4,6-trimethylphenyl)benzamide

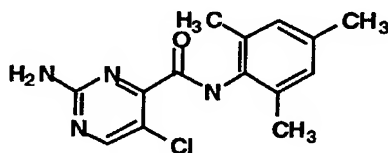


20

Compound **368** was prepared by an analogous method as that of **3**, except using 2-methyl-5-nitrobenzoic acid to give the title compound **368** as a
 white solid.

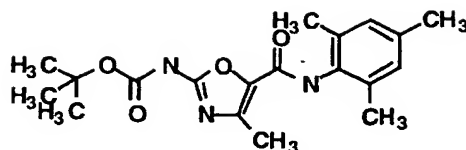
Example 369Preparation of 5-Amino-2-methyl-N-(2,4,6-trimethylphenyl)benzamide

- 5 10% Palladium on charcoal (30 mg) was added to a stirred solution of 368 (149 mg, 0.5 mmol) in EtOAc (50 mL). The reaction flask was equipped with a hydrogen filled balloon via a three-way stopcock. Air inside the flask was evacuated under reduced pressure and the flask filled with hydrogen from the balloon. After 4 h, the catalyst was filtered, washed
- 10 with EtOAc (5 mL, 5x). The filtrate was concentrated to obtain the title compound (133 mg, 99%) as a white solid.

Example 370Preparation of 2-Amino-5-chloro-N-(2,4,6-trimethylphenyl)- 4-pyrimidinecarboxamide

- Compound **370** was prepared by an analogous method as that of 3, except using 2-amino-5-chloro-pyrimidine-4-carboxylic acid to give the title
- 20 compound **370** as a white solid.

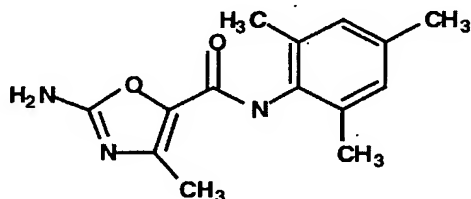
Example 371Preparation of [4-Methyl-5-[[[(2,4,6-trimethylphenyl)amino]carbonyl]- 2-oxazolyl]carbamic acid 1,1-dimethylethyl ester



Compound **371** was prepared by an analogous method as that of **1**, except using 2-*tert*-butoxycarbonyloxyamino-4-methyl-5-oxazolecarboxylic acid to give the title compound **371** as a light yellow foam.

Example 372

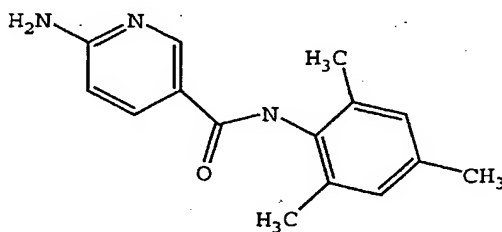
Preparation of 2-Amino-4-(methyl)-N-(2,4,6-trimethylphenyl)-5-oxazolecarboxamide, trifluoroacetate (1:1)



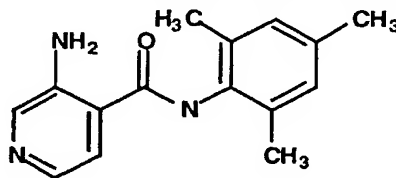
Compound **372** was prepared by an analogous method as that of **4**, except using **369** to give the title compound **372** as a white solid.

Example 373

Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-5-pyridinecarboxamide



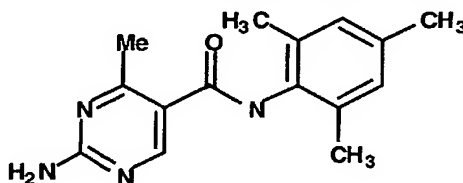
Compound **373** was prepared by an analogous method as that of **3**, except using 6-aminonicotinic acid to give the title compound **373** as a white solid.

Example 374Preparation 3-Amino-N-(2,4,6-trimethylphenyl)-4-pyridinecarboxamide

5

Compound **374** was prepared by an analogous method as that of **3**, except using 3-amino-4-pyridinecarboxylic acid to give the title compound **374** as a white solid.

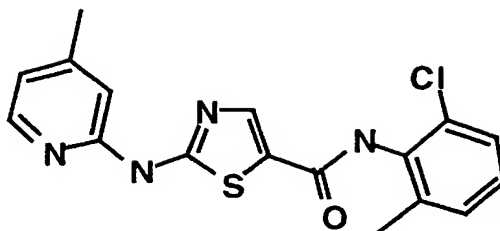
10

Example 375Preparation 2-Amino-4-methyl-N-(2,4,6-trimethylphenyl)-5-pyrimidinecarboxamide

15 Compound **375** was prepared by an analogous method as that of **3**, except using 2-amino-4-methyl-5-pyrimidinecarboxylic acid to give the title compound **375** as a white solid.

Example 376

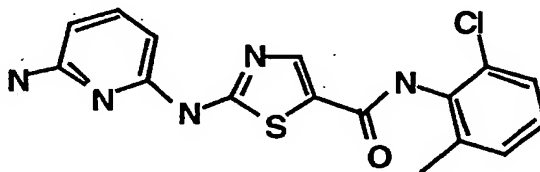
20 Preparation of N-(2-Chloro-6-methylphenyl)-2-[(4-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide



Compound **376** was prepared by an analogous method as that of **319B**,
except using 2-amino-4-methyl-pyridine to give the title compound **376** as
5 an off-white solid.

Example 377

Preparation of 2-[(6-Amino-2-pyridinyl)amino]-N-(2-chloro-6-
methylphenyl)-5-thiazolecarboxamide



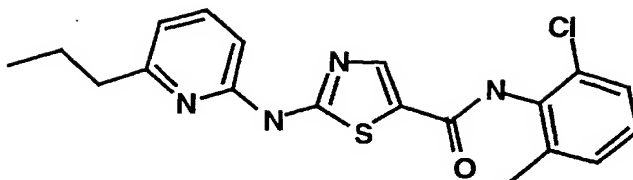
10

Compound **377** was prepared by an analogous method as that of **319B**,
except using 2,6-diaminopyridine to give the title compound **377** as a light
brown solid solid.

15

Example 378

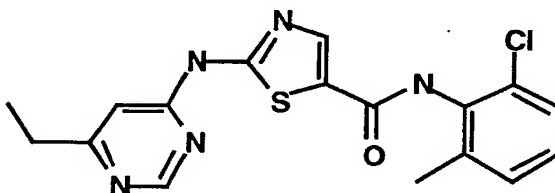
Preparation of N-(2-Chloro-6-methylphenyl)-2-[(6-propyl-2-
pyridinyl)amino]-5-thiazolecarboxamide



Compound **378** was prepared by an analogous method as that of **319B**,
except using 2-amino-6-propyl-pyridine to give the title compound **378** as
5 an off-white solid.

Example 379

Preparation of N-(2-Chloro-6-methylphenyl)-2-[(6-ethyl-4-
pyrimidinyl)amino]-5-thiazolecarboxamide



Compound **379** was prepared by an analogous method as that of **319B**,
except using 4-amino-6-ethyl-pyrimidine to give the title compound **379** as
a white solid.

Examples 380 to 409

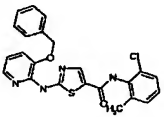
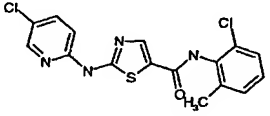
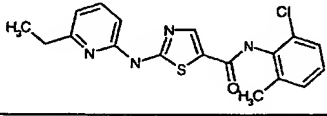
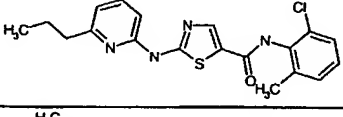
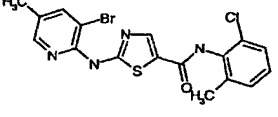
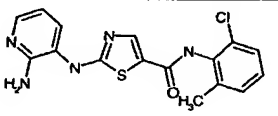
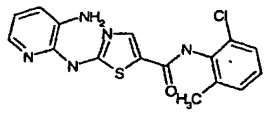
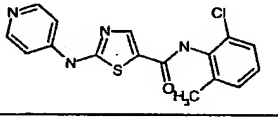
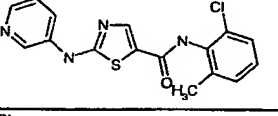
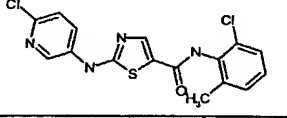
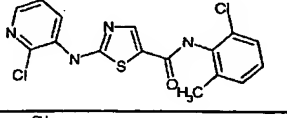
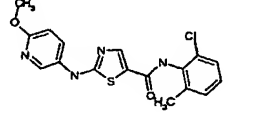
General Procedure

20 Compounds 380 to 409 were prepared by an analogous method as that of
319B. For the following examples 380 to 527 "HPLC Ret Time" is the
HPLC retention time under the following conditions: YMC S5 ODS 4.6 x
50 mm Ballastic Column, 4 min gradient starting from 100% solvent A

(10% MeOH, 90% H₂O, 0.2% H₃PO₄) to 100% solvent B (90% MeOH, 10% H₂O, 0.2% H₃PO₄), flow rate 4 mL/min, λ = 220 nM. Where used, "HPLC Ret Time 'B'" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 33 mm Turbo Column, 2 min gradient starting from

5 100% solvent A (10% MeOH, 90% H₂O, 0.1% TFA) to 100% solvent B (90% MeOH, 10% H₂O, 0.1% TFA) with 1min at 100% solvent B, flow rate 4 mL/min, λ = 220 nM.

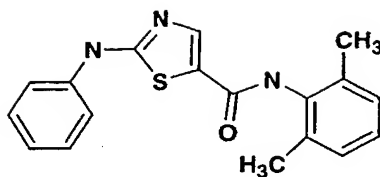
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
380		'N-(2-Chloro-6-methylphenyl)-2-(2-pyridinylamino)-5-thiazolecarboxamide	3.337
381		'N-(2-Chloro-6-methylphenyl)-2-[(6-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.61
382		'N-(2-Chloro-6-methylphenyl)-2-[(5-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.487
383		'N-(2-Chloro-6-methylphenyl)-2-[(4-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.293
384		'N-(2-Chloro-6-methylphenyl)-2-[(3-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.243
385		'2-[(5-Bromo-3-methyl-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	4.17
386		'2-[(6-Amino-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	2.817
387		'2-[(5-Bromo-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-	4.023

		thiazolecarboxamide	
388		'N-(2-Chloro-6-methylphenyl)-2-[[3-(phenylmethoxy)-2-pyridinyl]amino]-5-thiazolecarboxamide	4.143
389		'N-(2-Chloro-6-methylphenyl)-2-[(5-chloro-2-pyridinyl)amino]-5-thiazolecarboxamide	3.957
390		'N-(2-Chloro-6-methylphenyl)-2-[(6-ethyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.867
391		'N-(2-Chloro-6-methylphenyl)-2-[(6-propyl-2-pyridinyl)amino]-5-thiazolecarboxamide	4.083
392		'2-[(3-Bromo-5-methyl-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	4.077
393		'2-[(2-Amino-3-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	2.343
394		'2-[(3-Amino-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	2.777
395		'N-(2-Chloro-6-methylphenyl)-2-(4-pyridinylamino)-5-thiazolecarboxamide	2.493
396		'N-(2-Chloro-6-methylphenyl)-2-(3-pyridinylamino)-5-thiazolecarboxamide	2.47
397		'N-(2-Chloro-6-methylphenyl)-2-[(6-chloro-3-pyridinyl)amino]-5-thiazolecarboxamide	3.75
398		'N-(2-Chloro-6-methylphenyl)-2-[(2-chloro-3-pyridinyl)amino]-5-thiazolecarboxamide	3.443
399		'N-(2-Chloro-6-methylphenyl)-2-[(6-methoxy-3-pyridinyl)amino]-5-thiazolecarboxamide	3.517

400		'N-(2-Chloro-6-methylphenyl)-2-[(3,5-dimethyl-2-pyrazinyl)amino]-5-thiazolecarboxamide	3.583
401		'N-(2-Chloro-6-methylphenyl)-2-(phenylamino)-5-thiazolecarboxamide	3.697
402		'N-(2-Chloro-6-methylphenyl)-2-[(3-ethylphenyl)amino]-5-thiazolecarboxamide	4.107
403		'N-(2-Chloro-6-methylphenyl)-2-[(3,5-dimethylphenyl)amino]-5-thiazolecarboxamide	3.98
404		'N-(2-Chloro-6-methylphenyl)-2-[(4,6-dimethyl-2-pyrimidinyl)amino]-5-thiazolecarboxamide	3.51
405		'N-(2-Chloro-6-methylphenyl)-2-[(6-ethyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide	2.943
406		'N-(2-Chloro-6-methylphenyl)-2-[(6-chloro-2-pyrazinyl)amino]-5-thiazolecarboxamide	3.763
407		2-[(3-Aminophenyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	2.633
408		'N-(2-Chloro-6-methylphenyl)-2-[(3-hydroxyphenyl)amino]-5-thiazolecarboxamide	3.337
409		2-[(3-Bromophenyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	4.12

Example 410

Preparation of 'N-(2,6-Dimethylphenyl)-2-(phenylamino)-5-thiazolecarboxamide



A. [5-[(2,6-dimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

- 5 Compound **410A** was prepared by an analogous method as that of **315C**, except using 2,6-dimethylaniline.

B. 2-Amino-N-(2,6-dimethylphenyl)- 5-thiazolecarboxamide

- 10 Compound **410B** was prepared by an analogous method as that of **315D**, except using compound **410A**.

C. Title Compound

- The title compound was prepared by an analogous method as that of **319B**, except using compound **410B** and aniline. HPLC Ret. Time
15 3.69min.

Examples 411 to 427

20 **General Procedure**

Compounds **411** to **427** were prepared by an analogous method as that of **319B**.

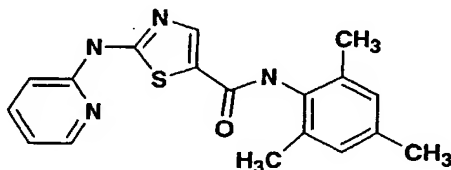
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
411		'N-(2,6-Dimethylphenyl)-2-(methylphenylamino)-5-thiazolecarboxamide	3.667
412		'N-(2,6-Dimethylphenyl)-2-(2-pyridinylamino)-5-thiazolecarboxamide	3.297
413		'N-(2,6-Dimethylphenyl)-2-[(6-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.587
414		'N-(2,6-Dimethylphenyl)-2-[(4-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.222
415		'N-(2,6-Dimethylphenyl)-2-[(4-ethyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.54
416		'N-(2,6-Dimethylphenyl)-2-[(4,6-dimethyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.543
417		'2-[(6-Amino-2-pyridinyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide	2.807
418		'N-(2,6-Dimethylphenyl)-2-[(6-ethyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.847
419		'N-(2,6-Dimethylphenyl)-2-[(6-propyl-2-pyridinyl)amino]-5-thiazolecarboxamide	4.057
420		'2-[(2-Amino-3-pyridinyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide	2.337
421		'2-[(3-Amino-2-pyridinyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide	2.737

422		'2-[(6-Amino-2-methyl-4-pyrimidinyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide	2.71
423		'N-(2,6-Dimethylphenyl)-2-[[6-(4-morpholinyl)-3-pyridazinyl]amino]-5-thiazolecarboxamide	2.727
424		'2-[(6-Chloro-3-pyridazinyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide	3.46
425		'N-(2,6-Dimethylphenyl)-2-(3-pyridazinylamino)-5-thiazolecarboxamide	2.973
426		'2-[(3-Aminophenyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide	2.63
427		'2-[(3-Bromophenyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide	4.143

Example 428

Preparation of '2-(2-Pyridinylamino)-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide

5



- A. [5-[[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid,
10 1,1-dimethylethyl ester

Compound 428A was prepared by an analogous method as that of 315C, except using 2,4,6-trimethylaniline.

B. 2-Amino-N-(2,6-dimethylphenyl)- 5-thiazolecarboxamide

Compound **428B** was prepared by an analogous method as that of **315D**, except using compound **428A**.

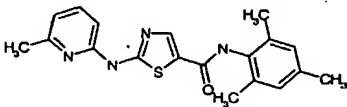
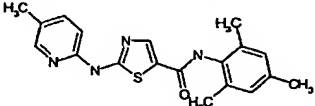
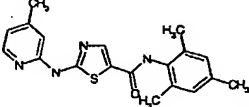
5 C. Title Compound

The title compound was prepared by an analogous method as that of **319B**, except using compound **428B** and 2-aminopyridine. HPLC Ret. Time 3.66min.

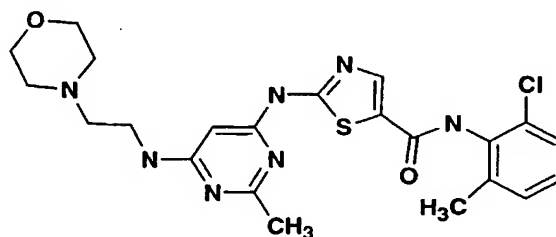
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Examples 429 to 443**15 General Procedure**

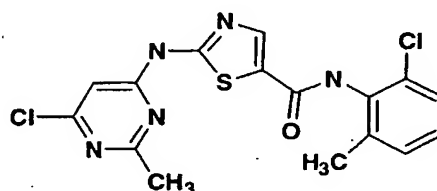
Compounds **429** to **443** were prepared by an analogous method as that of **319B**.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
429		2-[(6-Methyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.903
430		2-[(5-Methyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.8
431		2-[(4-Methyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.603

432		'2-[(3-Methyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.56
433		'2-[(5-Bromo-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.263
434		'2-[(5-Chloro-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.203
435		'2-[(6-Methoxy-3-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.8
436		'2-[(4-Ethyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.86
437		'2-[(6-Ethyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.127
438		'2-[(6-Chloro-3-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.017
439		'2-[(2,6-Dimethyl-4-pyrimidinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	2.943
440		'2-[(4-Methyl-2-pyrimidinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.723
441		'2-(2-Pyrazinylamino)-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.65
442		'2-[(6-Chloro-2-pyrazinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.05
443		'2-[(3,5-Dimethyl-2-pyrazinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.877

Example 444Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[[2-(4-morpholinyl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide

5

A

- 10 To a suspension of NaH (148mg, 6.17mmol) in THF (20mL) was added a solution of compound **315D** (551mg, 2.06mmol) in THF (10mL) and stirred at RT for 0.5h. A solution of 4,6-dichloro-2-methylpyrimidine (671.6mg, 4.12mmol) in THF (10mL) and stirred at RT overnight. The reaction was quenched with acetic acid and the solvent removed in vacuo. Water and
- 15 saturated NaHCO₃ were added to the residue and extracted with CH₂Cl₂. The organic layer was removed in vacuo and the crude material purified by column chromatography to give **444A** (494mg).

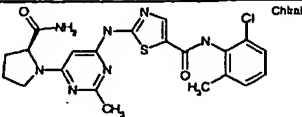
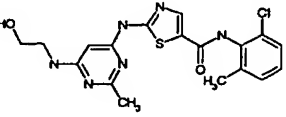
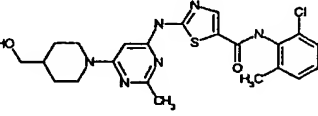
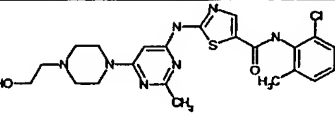
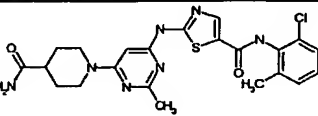
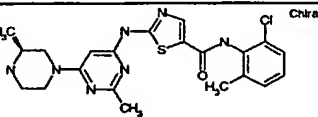
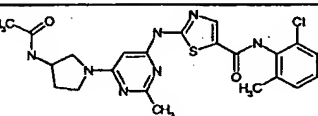
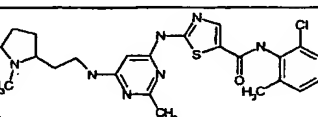
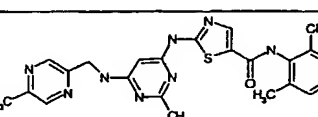
B. Title Compound

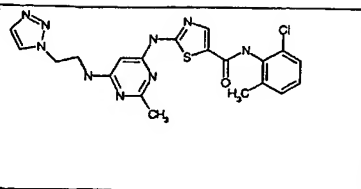
- 20 To compound **444A** (30mg) was added N-(2-aminoethyl)-morpholine (300μL) and the mixture was heated at 80°C for 2h. Water was added to the reaction and the product was collected by filtration. HPLC Ret. Time 2.357min.

Examples 445 to 461**General Procedure**

- 5 Compounds **445** to **461** were prepared by an analogous method as that of **444B** by substituting the appropriate amine.

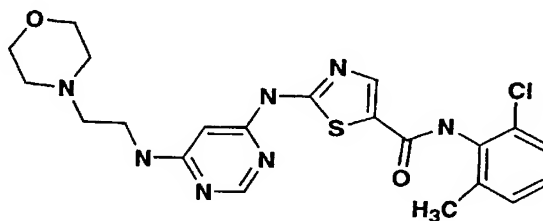
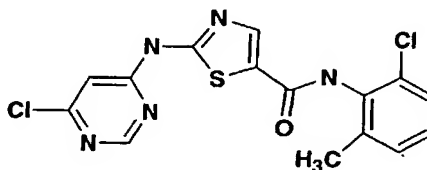
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
445		'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[[3-(4-morpholinyl)propyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.253
446		'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[methyl[3-(methylamino)propyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.493
447		'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[[2-(tetrahydro-2-oxo-1H-imidazol-1-yl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.71
448		'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[(2-1H-imidazol-4-ylethyl)amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.303
449		'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-(4-morpholinyl)-4-pyrimidinyl]amino]-5-thiazolecarboxamide	3.337
450		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[(2R)-1-ethyl-2-pyrrolidinyl]methyl]amino]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.703
451		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[(2S)-1-ethyl-2-pyrrolidinyl]methyl]amino]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.717

		methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide	
452		'2-[[6-[(2S)-2-(Aminocarbonyl)-1-pyrrolidinyl]-2-methyl-4-pyrimidinyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	2.81
453		'N-(2-Chloro-6-methylphenyl)-2-[[6-[(2-hydroxyethyl)amino]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.677
454		'N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(hydroxymethyl)-1-piperidinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide	3.05
455		'N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.717
456		'1-[6-[[5-[(2-Chloro-6-methylphenyl)amino]carbonyl]-2-thiazolyl]amino]-2-methyl-4-pyrimidinyl]-4-piperidinecarboxamide	2.863
457		'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[(3S)-3-methyl-1-piperazinyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.823
458		'2-[[6-[3-(Acetylamino)-1-pyrrolidinyl]-2-methyl-4-pyrimidinyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	2.78
459		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(1-methyl-2-pyrrolidinyl)ethyl]amino]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.383
460		'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[(5-methyl-2-pyrazinyl)methyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	3.027

461		'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[[2-(1H-1,2,3-triazol-1-yl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide 2.78
-----	---	--

Example 462

5 Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(4-morpholinyl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide

A

Compound **462A** was prepared by an analogous method as that of **444A**, except using 4,6-dichloropyrimidine.

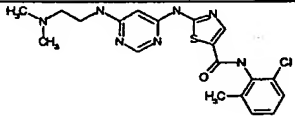
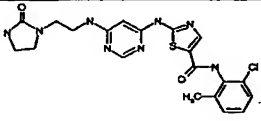
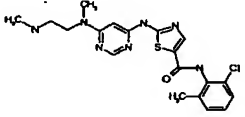
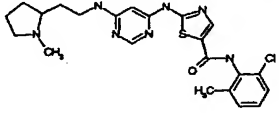
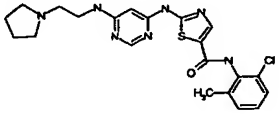
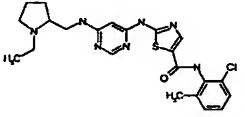
15 **B. Title Compound**

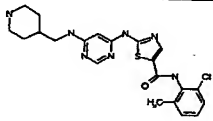
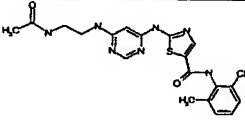
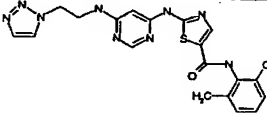
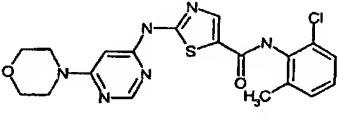
The title compound was prepared by an analogous method as that of **444B**, except using compound **462A** in place of compound **444A**. HPLC Ret. Time 2.553min.

20 Examples 463 to 472

General Procedure

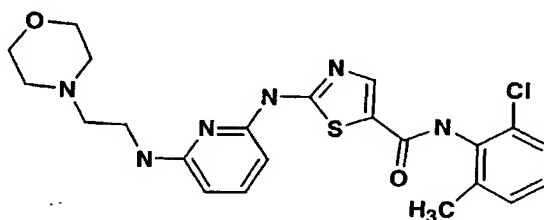
Compounds **463** to **472** were prepared by an analogous method as that of **444B** by substituting the appropriate amine. "HPLC Ret Time 'B'" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 33 mm Turbo Column, 2 min gradient starting from 100% solvent A (10% MeOH, 90% H₂O, 0.1% TFA) to 100% solvent B (90% MeOH, 10% H₂O, 0.1% TFA) with 1min at 100% solvent B, flow rate 4 mL/min, λ = 220 nM.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
463		'N-(2-Chloro-6-methylphenyl)-2-[[[6-[[2-(dimethyl-amino)-ethyl]amino]-4-pyrimidinyl]-amino]-5-thiazolecarboxamide	2.527
464		'N-(2-Chloro-6-methylphenyl)-2-[[[6-[[2-(tetrahydro-2-oxo-1H-imidazol-1-yl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.797
465		'N-(2-Chloro-6-methylphenyl)-2-[[[6-[methyl[2-(methylamino)-ethyl]amino]-4-pyrimidinyl]-amino]-5-thiazolecarboxamide	1.137 B
466		'N-(2-Chloro-6-methylphenyl)-2-[[[6-[[2-(1-methyl-2-pyrrolidiny)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	1.113 B
467		'N-(2-Chloro-6-methylphenyl)-2-[[[6-[[2-(1-pyrrolidiny)ethyl]amino]-4-pyrimidinyl]-amino]-5-thiazolecarboxamide	1.150 B
468		'N-(2-Chloro-6-methylphenyl)-2-[[[6-[[[(1-ethyl-2-pyrrolidiny)methyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	1.237 B

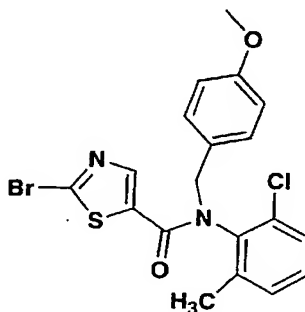
469		'N-(2-Chloro-6-methylphenyl)-2-[[6-[(4-piperidinyl-methyl)amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	1.160 B
470		'2-[[6-[[2-(Acetylamino)-ethyl]amino]-4-pyrimidinyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	2.457 B
471		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(1H-1,2,3-triazol-1-yl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.897
472		'N-(2-Chloro-6-methylphenyl)-2-[[6-(4-morpholinyl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	3.437

Example 473Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(4-morpholinyl)ethyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide

5

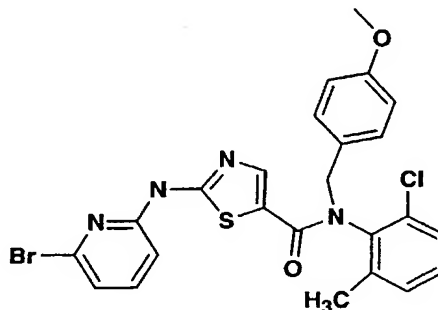


A.



To a suspension of NaH (2.83g, 118mmol) in DMF (350mL) cooled to 0°C was added compound **319A** (31g, 93.5mmol). The mixture was stirred for 45min at 0°C then Bu₄NI (6.9g, 18.7mmol) was added followed by addition of 4-methoxy benzylchloride (18g, 115mmol). The reaction was allowed to warm to RT. After stirring overnight at RT the reaction was quenched slowly with acetic acid then the solvent removed in vacuo. To the residue was added water and neutralized with saturated aqueous NaHCO₃. The mixture was extracted 3 times with EtOAc and the combined organic layers washed with water then washed with saturated NaCl solution. The EtOAc layer was concentrated in vacuo and the residue purified by column chromatography to give **473A** (35g).

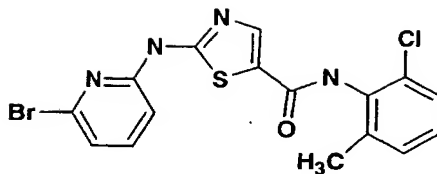
B



15

To compound **473A** (0.5g, 1.1mmol) dissolved in THF (50mL) was slowly added NaH (0.13g, 5.5mmol) followed by 2-bromo-6-aminopyridine (0.76g, 4.4mmol). The reaction was heated to reflux for 2h then cooled to RT and quenched with acetic acid. The solvent was removed in vacuo then water and hexane was added and stirred at RT. The solid precipitate was collected by filtration and washed with water and Et₂O to give **473B** (0.48g)

C



To compound **473B** (0.48g) dissolved in TFA (5mL) was added anisole
 5 (2mL) followed by triflic acid (1mL). The reaction was stirred at RT for 3h
 then was slowly added to a rapidly stirred mixture of ice, saturated
 NaHCO₃, Et₂O and CH₂Cl₂. The mixture was stirred cold for 1h then the
 solid precipitate was collected by filtration and washed with water
 followed by Et₂O/CH₂Cl₂ mixture to give **473C** (0.344g). HPLC Ret. Time
 10 3.85min.

D. Title Compound

The title compound was prepared by an analogous method as that of
444B, except using compound **473C** in place of compound **444A**. HPLC
 15 Ret. Time 2.80min.

Examples 474 to 480

General Procedure

20

Compounds **474** to **480** were prepared by an analogous method as that of
473D by substituting the appropriate amine.

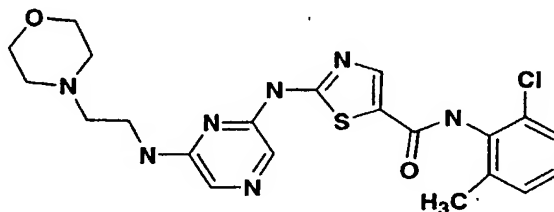
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
474		N-(2-Chloro-6-methylphenyl)- 2-[[6-[[3-(4-morpholinyl)- propyl]amino]-2-pyridinyl]- amino]-5-thiazolylcarboxamide	2.867

475		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[3-(methylamino)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	3.067
476		'N-(2-Chloro-6-methylphenyl)-2-[[6-[(3S)-3-methyl-1-piperazinyl]-2-pyridinyl]amino]-5-thiazolecarboxamide	2.827
477		'N-(2-Chloro-6-methylphenyl)-2-[[6-[(3-1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	2.83
478		'N-(2-Chloro-6-methylphenyl)-2-[[6-[(2-hydroxyethyl)amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	3.077
479		'N-(2-Chloro-6-methylphenyl)-2-[[6-[(2-1H-imidazol-1-ylethyl)amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	2.903
480		'N-(2-Chloro-6-methylphenyl)-2-[[6-(4-morpholinyl)-2-pyridinyl]amino]-5-thiazolecarboxamide	3.727

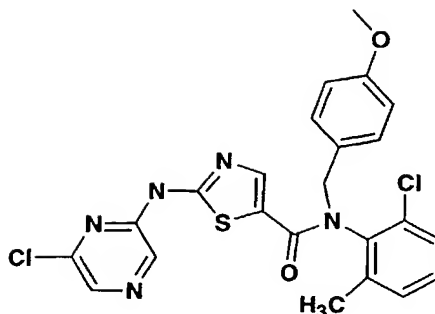
Example 481

Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(4-morpholinyl)ethyl]amino]-2-pyrazinyl]amino]-5-thiazolecarboxamide

5

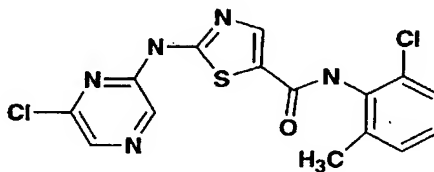


A.



Compound **481A** was prepared by an analogous method as that of **473B**,
except using compound 2-chloro-6-aminopyrazine in place of compound 2-
5 bromo-6-aminopyridine.

B. (alternate synthesis for compound 406)



Compound **406** was prepared by an analogous method as that of **473C**,
except using compound **481A** in place of compound **473B**.

C. Title Compound

The title compound was prepared by an analogous method as that of
444B, except using compound **406** in place of compound **444A**. HPLC Ret.
Time 2.69min.

Examples 482 to 486**General Procedure**

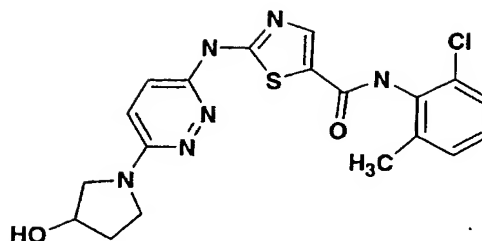
- 5 Compounds **482** to **486** were prepared by an analogous method as that of **481C** by substituting the appropriate amine.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
482		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[3-(4-morpholinyl)propyl]amino]-2-pyrazinyl]amino]-5-thiazolecarboxamide	2.783
483		'N-(2-Chloro-6-methylphenyl)-2-[[6-(4-morpholinyl)-2-pyrazinyl]amino]-5-thiazolecarboxamide	3.57
484		'N-(2-Chloro-6-methylphenyl)-2-[[6-[(3S)-3-methyl-1-piperazinyl]-2-pyrazinyl]amino]-5-thiazolecarboxamide	2.743
485		'N-(2-Chloro-6-methylphenyl)-2-[[6-(3-hydroxy-1-pyrrolidinyl)-2-pyrazinyl]amino]-5-thiazolecarboxamide	3.327
486		'N-(2-Chloro-6-methylphenyl)-2-[[6-(1H-imidazol-1-yl)-2-pyrazinyl]amino]-5-thiazolecarboxamide	2.68

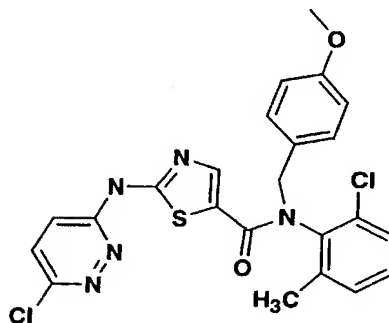
10

Example 487

Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[6-(3-hydroxy-1-pyrrolidinyl)-3-pyridazinyl]amino]-5-thiazolecarboxamide

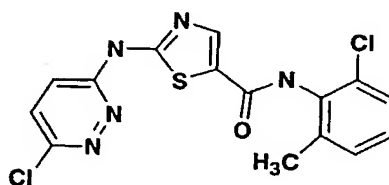


A.



5

Compound **487A** was prepared by an analogous method as that of **473B**, except using compound 3-chloro-5-aminopyridazine in place of compound 2-bromo-6-aminopyridine.

10 B

Compound **487B** was prepared by an analogous method as that of **473C**,
 15 except using compound **487A** in place of compound **473B**.

C. Title Compound

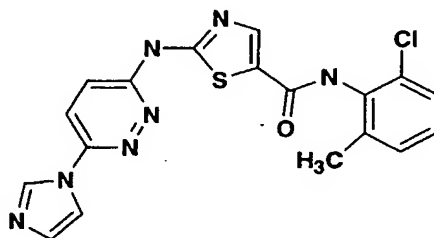
The title compound was prepared by an analogous method as that of **444B**, except using compound **487B** in place of compound **444A**, and 3-hydroxypyrrolidine in place of N-(2-aminoethyl)-morpholine. HPLC Ret. Time 2.493min.

5

Example 488

Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[6-(1H-imidazol-1-yl)-3-pyridazinyl]aminol-5-thiazolecarboxamide

10



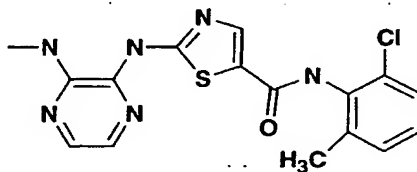
Compound **488** was prepared by an analogous method as that of **487C**, except using imidazole in place of 3-hydroxypyrrolidine. HPLC Ret. Time 2.61min.

15

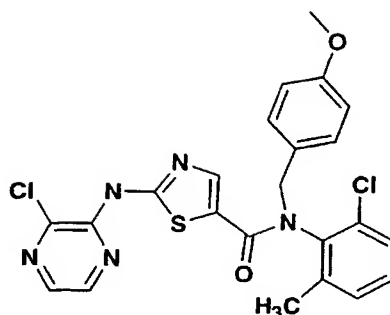
Example 489

Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[3-(methylamino)-2-pyrazinyl]aminol-5-thiazolecarboxamide

20

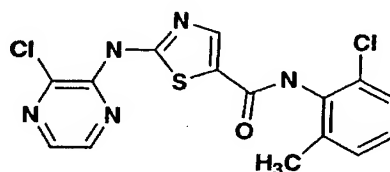


A.



Compound **489A** was prepared by an analogous method as that of **473B**,
except using compound 2-chloro-3-aminopyrazine in place of compound 2-
5 bromo-6-aminopyridine.

B



10 Compound **489B** was prepared by an analogous method as that of **473C**,
except using compound **489A** in place of compound **473B**.

C. Title Compound

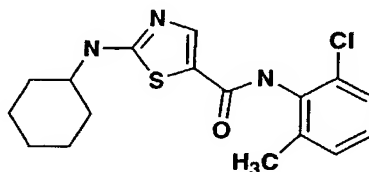
15 The title compound was prepared by an analogous method as that of
444B, except using compound **489B** in place of compound **444A**, and using
methylamine in place of N-(2-aminoethyl)-morpholine. HPLC Ret. Time
2.81min.

20

Examples 490 to 494**General Procedure**

- 5 Compounds **490** to **494** were prepared by an analogous method as that of **489C** by substituting the appropriate amine.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
490		N-(2-Chloro-6-methylphenyl)-2-[[3-(3-hydroxy-1-pyrrolidinyl)-2-pyrazinyl]amino]-5-thiazolecarboxamide	2.82
491		N-(2-Chloro-6-methylphenyl)-2-[[3-(cyclopropylamino)-2-pyrazinyl]amino]-5-thiazolecarboxamide	2.94
492		N-(2-Chloro-6-methylphenyl)-2-[[3-(4-morpholinyl)-2-pyrazinyl]amino]-5-thiazolecarboxamide	3.643
493		N-(2-Chloro-6-methylphenyl)-2-[[3-[[2-(4-morpholinyl)ethyl]amino]-2-pyrazinyl]amino]-5-thiazolecarboxamide	2.72
494		2-[[3-[[2-(Acetylamino)ethyl]amino]-2-pyrazinyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	2.933

Example 495Preparation of 'N-(2-Chloro-6-methylphenyl)-2-(cyclohexylamino)-5-thiazolecarboxamide

5

Compound **495** was prepared by an analogous method as that of **444B**, except using compound **319A** in place of compound **444A**, and using cyclohexylamine in place of N-(2-aminoethyl)-morpholine. HPLC Ret.

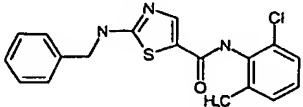
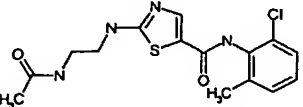
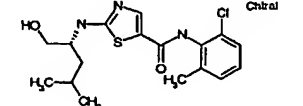
10 Time 3.547min.

Examples 496 to 500**15 General Procedure**

Compounds **496** to **500** were prepared by an analogous method as that of **495** by substituting the appropriate amine.

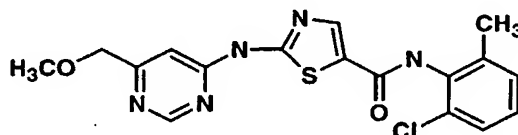
20

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
496		'N-(2-Chloro-6-methylphenyl)-2-(methylamino)-5-thiazolecarboxamide	2.357
497		'N-(2-Chloro-6-methylphenyl)-2-(cyclopropylamino)-5-thiazolecarboxamide	2.887

498		'N-(2-Chloro-6-methylphenyl)-2-[(phenylmethyl)amino]-5-thiazolecarboxamide	3.500
499		'2-[[2-(Acetylamino)ethyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	2.483
500		'N-(2-Chloro-6-methylphenyl)-2-[[[(1R)-1-(hydroxymethyl)-3-methylbutyl]amino]-5-thiazolecarboxamide	3.407

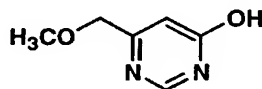
Example 501

5 Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[6-(methoxymethyl)-4-pyrimidinyl]amino]-5-thiazolecarboxamide



10

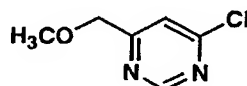
A



- 15 To the mixture of methyl 4-methoxyacetoacetate (14.6 g, 0.1 mol) and formami-dine hydrogen chloride salt (16.1 g, 0.2 mol) in 70 mL of dry MeOH was added a 25% solution of sodium methoxide (70 mL, 0.3 mol) in MeOH portionwise. A white precipitate was formed immediately. The reaction mixture was stirred at room temperature for 1.0 hr. Acetic acid

(28.6 mL, 0.5 mol) was added and the reaction mixture was concentrated in vacuo. Water was added to the residue and the mixture was supersaturated with NaCl and extracted with EtOAc (x5). Combined extracts were dried over anhydrous Na₂SO₄ and concentrated in vacuo to
5 give 8.13 g of compound **501A** as a yellow solid.

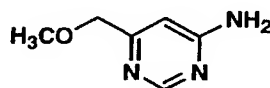
B



10

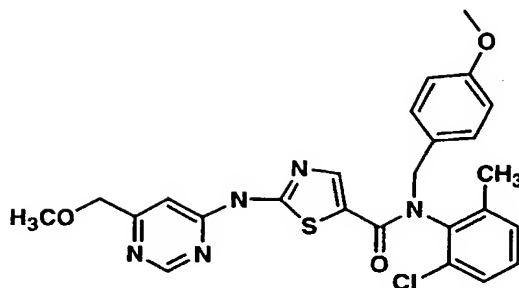
The mixture of compound **501A** (5.3 g, 37.8 mmol) and POCl₃ (40 mL) was heated to reflux for 2.0 hrs. Concentration in vacuo and the residue was poured into a mixture of ice-CH₂Cl₂. The pH was adjusted to 6.5 to 7 using concentrated NH₄OH. The mixture was extracted with CH₂Cl₂ (x3) and
15 combined extracts were dried over Na₂SO₄. Concentration in vacuo followed by flash chromatography (CH₂Cl₂-EtOAc: 9:1) on silica gel gave 5.33 g of compound **501B** as a pale yellow oil.

20 C



The mixture of compound **501B** (3.2 g, 20 mmol) and NH₄OH (50 mL) was heated to 85.C in a pressure tube for 3.0 hrs. After cooled to room
25 temperature, the reaction mixture was concentrated in vacuo and the residue was triturated with ether to give 2.81 g of compound **501C** as a pale yellow solid.

D



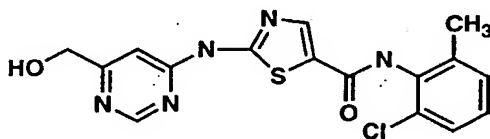
- 5 Compound **501D** was prepared from compound **501C** by a method analogous to that used for the preparation of compound **473B**.

E Title Compound

- 10 The title compound was prepared from compound **501D** by a method analogous to that used for the preparation of compound **473C**. HPLC Retention time = 3.25 min.

Example 502

- 15 Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[6-(hydroxymethyl)-4-pyrimidinyl]amino]-5-thiazolecarboxamide



- 20 To a solution of compound **501** (56 mg, 0.144 mmol) in dry CH_2Cl_2 (3.0 mL) cooled at 0°C was added neat BBr_3 (0.054 mL, 0.574 mmol). The mixture was stirred for 1.0 hr at ambient temperature. MeOH was added slowly with care at 0°C and the resulting mixture was concentrated in

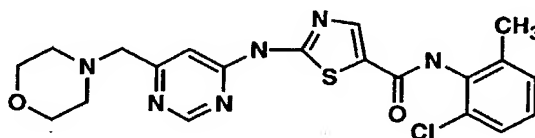
vacuo. Water was added to the residue and pH was adjusted to 7 with Sat'd NaHCO₃. The white precipitate was collected by filtration, rinsed with water/ether and dried under high vacuum to give 52 mg of Compound **502** as an off-white solid. HPLC Retention time = 2.84 min.

5

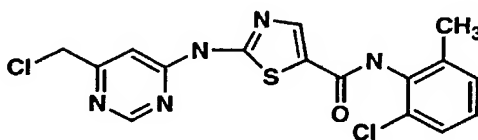
Example 503

Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[6-(4-morpholinylmethyl)-4-pyrimidinyl]aminol]-5-thiazolecarboxamide

10



A



15

To a suspension of compound **502** (44.2 mg, 0.118 mmol) in 0.5 mL of dry CH₂Cl₂ was added thionyl chloride (0.086 mL, 1.18 mmol). The reaction mixture was stirred for 5.0 hrs. Concentration in vacuo and the residue was azeotropic evaporated with CH₂Cl₂ to give 56 mg of **503** as an yellow solid.

20

B Title Compound

The mixture of compound **503A** (20 mg), morpholine (0.014 mL) and diisopropylethyl amine (0.09 mL) in 0.5 mL of dry dioxane was heated to

25

85.C for 4.0 hrs. Concentration in vacuo followed by flash chromatography (CH_2Cl_2 -MeOH- NH_4OH : 95:5:0.5) on silica gel gave 15 mg of title compound as an off-white solid.

HPLC Retention time = 2.52 min.

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Examples 504 to 513

General Procedure

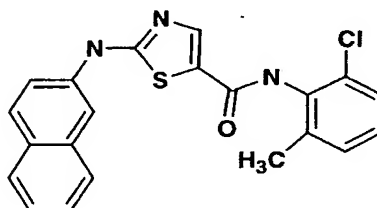
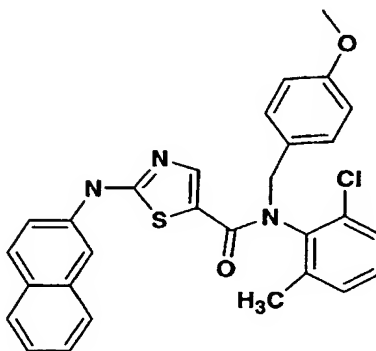
- 10 Compounds **504** to **513** were prepared from **503A** by a route analogous to that used for the preparation of **503**. The compounds of these examples have the structure:

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
504		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[2-(dimethylamino)ethyl]amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.083
505		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[2-(4-morpholinyl)ethyl]amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.593
506		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[3-(4-morpholinyl)propyl]amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.163
507		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[3-(2-oxo-1-pyrrolidinyl)propyl]amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.693
508		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[2-(1H-imidazol-4-ylethyl)amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.143
509		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[3-(1H-imidazol-1-yl)propyl]amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	1.103 B
510		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[2-(2-pyridinyl)ethyl]amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	1.113 B
511		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[2-(3-pyridinyl)ethyl]amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	1.117 B

512		'1-[[6-[[5-[[2-Chloro-6-methylphenyl]amino]carbonyl]-2-thiazolyl]amino]-4-pyrimidinyl]methyl]-4-piperidinecarboxamide	1.207 B
513		'2-[[6-[[2-(Acetylamino)ethyl]amino]methyl]-4-pyrimidinyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	1.193 B

Example 514Preparation of N-(2-Chloro-6-methylphenyl)-2-(2-naphthalenylamino)-5-thiazolecarboxamide

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10 A

Compound **514A** was prepared from **473A** by an analogous method as that of **473B**, except using 2-aminonaphthalene in place of 2-bromo-6-aminopyridine.

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B. Title Compound

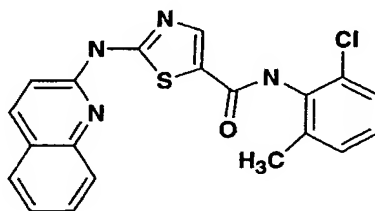
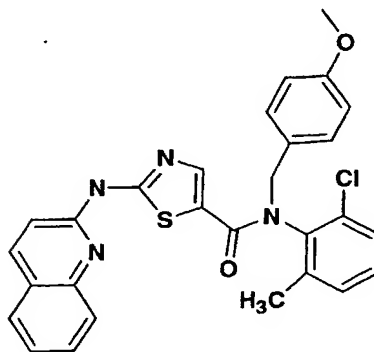
The title compound was prepared by an analogous method as that of **473C**, except using compound **514A** in place of compound **473B**. HPLC Ret. Time 4.11min.

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Example 515

Preparation of 'N-(2-Chloro-6-methylphenyl)-2-(2-quinolinylamino)-5-thiazolecarboxamide

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